Henry Ford Hospital Medical Bulletin

Vol. 6 June, 1958 No. 2

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Address communications to: Chairman, Publications Committee, The Henry Ford Hospital, Detroit, Michigan.

HENRY FORD HOSPITAL MEDICAL BULLETIN

Published quarterly by the Professional Staff of the
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Vol. 6 June, 1958 No. 2

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1958

THE MECHANISM, CHARACTERISTICS AND POTENTIAL OF THE BETA-EXCITED X-RAY SOURCE

LUTHER E. PREUSS, M. S.*

PREFACE:

The beta-excited X-ray utilizes the very familiar phenomena of bombardment of some target material in order to effect the production of useful photons of electromagnetic energy. The vacuum X-ray tube accomplishes this with the conventional cathode-ray which strikes the anode at high energies. The beta-excited device, however, is unique in that it has no need for the Coolidge vacuum tube and complex associated circuitry, but simply utilizes the beta particles emanating from certain radioactive isotopes during their transition. In the case of either the conventional mechanism or the beta-excited principle; 'white radiation' or *bremsstrahlung* as well as the *characteristic radiation* of the target material results from the target-electron interaction. These two components of the electromagnetic radiation may be utilized together, or the bremsstrahlung discriminated against as in X-ray diffraction, and the characteristic radiation specifically applied to analysis, absorptimetry, or radiography. The conventional X-ray system in its present fine stage of perfection has the advantages of high intensity, short exposure times and commercial adaptation to most problems in radiography, therapeutic and diagnostic radiology and analysis. However, the conventional X-ray generator suffers from the disadvantages of bulkiness, non-portability, need for intricacy of circuitry and electrical power source, and complex mechanical design. Such features are a distinct handicap in use in the field or for emergency application in remote areas where power is not available.

The beta-excited source, on the other hand, does present a new and intriguing potential for the special usages detailed above. The advent of the easily available pile produced syuthetic radionuclide has made possible valuable variations in its design. The source is small, stable and has zero power requirements. It is simple in construction and operation. It is easily portable and its reliability and stability makes its use in the field or in remote areas quite feasible. Such a source principle was investigated in this laboratory to evaluate its usefulness as a low energy, planar X-ray radiator for gross apposition radiography. The physical mechanism and development of such a planar source, as well as the small compound source-target is described herein.

The beta-excited source is, for the present, still a research tool and an intriguing study in physical design. It does, however, offer for the future some potential for a distinct type of X-ray source which eventually may find some direct application in radiography, radiology, analysis and testing.

This report consists of two prime sections. The first covers a review of the physical mechanisms extant in the source, the radionuclides applicable to the device, and their availability from the reactor, as well as some basic design features of the

*Edsel B. Ford Institute for Medical Research

source. The second portion details the characteristics of the specific beta-excited source developed and used experimentally in this laboratory. This will review some of the experimental results obtained with these sources by radiography and by gamma-ray recording scintillation spectrometer traces. This latter section concerns the experimental work done with a planar source design (termed the *apposition source*), plus some characteristics of the compound beta-excited source.

PART I

THE BETA EXCITATION MECHANISM:

The basic processes which are essential to all *direct* or *indirect* photon production, associated with the radioactive transition of the isotope, are: X-radiation through ionization, bremsstrahlung, internal conversion, photoelectric absorption, gamma emission, and pair production (see Table I). Initially, with the discovery of the naturally occurring radionuclides and later with the advent of the ubiquitous synthetic radioactive isotope, it was proposed that the simple gamma processes would compete with the cathode-ray tube methods of X-ray production, in the low and medium energy ranges. Evaluation of the energy characteristics of the gamma emitters (both natural and synthetic) showed their electromagnetic radiation to be generally too high for ordinary radiography, analysis and absorption studies. Not more than three nuclides show even theoretical application of their photon emission for the lower energies below 100 Kev. The beta-excited source, however, exhibits some potential in the lower energy regions by utilization and control of the two processes of bremsstrahlung and ionization.

TABLE I

PHOTON PRODUCTION PROCESSES*
ASSOCIATED WITH THE RADIONUCLIDE

1. X-radiation by Ionization.
2. Bremsstrahlung.
3. Internal Conversion.
4. Photoelectric Absorption.
5. Gamma Emission.
6. Pair Production.

*This listing includes secondary as well as primary photon production processes.

The radioactive isotope of thulium (Tm^{170}) has been studied in consequence of its 84 Kev photon and is a good example of direct photon emission. It provides one one of the few examples of moderately successful low energy photon application. Unfortunately Tm^{170} is not an example of simple low energy photon emission. Figure #1 is the decay scheme as given by Hollander, Perlman and Seaborg[1]. Branched-chain decay occurs with the production of two distinct beta spectra, (shown as diagonal arrows). The more energetic beta is .968 Mev and the weaker is .884 Mev. The

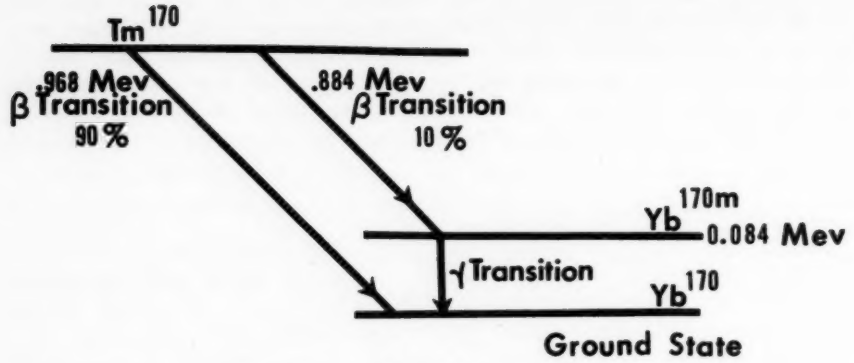

Figure 1

The simple thulium-170 transition is shown. The branched chain decay is through either the .968 Mev beta emission. This decay scheme is by Hollander, Perlman and Seaborg[4]. The .084 Mev gamma from the metastable Yb^{170m} is useful in study of production mechanisms and self absorption in the beta-excited source.

latter is followed by the 84 Kev photon from the excited Yb^{170m} daughter product. Study of the decay of this radionuclide has clarified some of the characteristics of the beta-excited mechanism which exists along with the simple photon emission from the metastable ytterbrium-170. Graham[2] has fixed 25% of the branched-chain decay as proceeding through the Yb^{170m} condition. The ground state is reached through emission of the 84 Kev photon or by internal conversion. According to Graham, this is a complex consisting of:

One; 0.084 Mev gamma radiation occurring with about 3% frequency.

Two; Yb K X-rays, 5% frequency.

Three; YB L and M X-rays, present in about 17% of the Tm^{170} transitions. Thus, emission, from the Tm^{170} falls into three categories.

(a) The two beta spectra.

(b) The 0.084 Mev gamma.

(c) The K, L and M shell YB^{170} X-rays.

This investigation of this radiation complex has provided an experimental basis for the study of varied aspects of the beta-excited source. The influence of changing source thickness, for Tm^{170} has been investigated by Liden and Starfeldt.[3] It was found that with increasing source thickness;

(1) The 84 Kev photon intensity rose to an asymptotic value which was imposed by the self-absorption of the source material which served as an internal shield.

(2) The relative percentage of Yb K X-rays decreased and the percentage of Tm K X-rays increased.

(3) The intensity of bremsstrahlung increased rapidly with increasing source thickness.

For source surface concentrations of 10^3 mg/cm^2, the intensity of bremsstrahlung was equal to that of the thulium K X-rays plus the ytterbium K X-rays.

The average 'white radiation' energy was around 100 Kev. This is a good example of the undesirable, high bremsstrahlung production rates which frequently 'smother' the desirable characteristic X-rays produced in the beta-excited X-ray source.

The primary components of the beta-excited photon source are essentially the same as those of the conventional X-ray device; much more simple in design detail. The requirements are; *first,* beta particles of the proper energy; *second,* an array of target atoms arranged in the beta flux for impingement by the particulate radiation.

Figure No. 2 describes schematically the two main mechanisms as well as one of several secondary phenomena. The radioactive isotope S, at the left, is the source of the beta particles (straight arrows) which impinge on the target volume T. Ejection of electrons through this collision process from the innermost electron shells results in *characteristic X-radiation* from the target atoms CX in the schematic). The second process of interest, consisting of the accelleration of the beta particle charge as it passes near the target atom nuclei, results in the continuous *white radiation,* or bremsstrahlung photon. This is designed as B. An important secondary effect is shown at the bottom of Figure No. 2. The beta particle charge is accellerated in the target T, which process results in the bremsstrahlung photon which is shown. This in turn interacts with the K shell of a target nuclei with the ejection of a planetary electron with the resulting production of a characteristic X-ray (CX) when this vacancy is filled. This fluorescence target radiation may be an important component of the total photons produced. In addition, these three phenomena may be supplemented by other combinations of photon production in the K, L and M target shells, as well as more complex effects through the fluorescence mechanism.

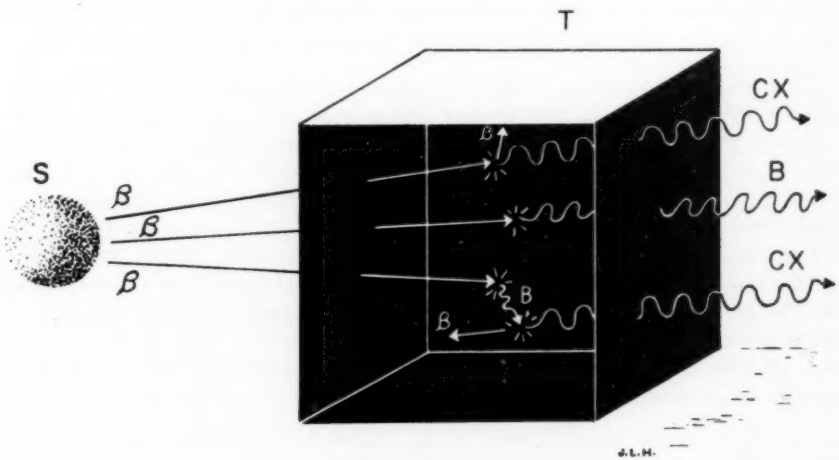

Figure 2

Some modes of production of X-radiation, by the beta-excited source are illustrated. *Characteristic X-ray* production is shown as CX. *Bremsstrahlung* production is shown as B, and the fluorescence photon process (CX at bottom) by the three-step mechanism on which bremsstrahlung B produced in T by the beta particle creates the characteristic radiation CX by interaction with the inner shell electrons of the target element.

The two physical mechanisms of *bremsstrahlung production* and *X-Ray production* may be separated into five separate modes (Table No. II). These are; *internal bremstrahlung, external bremsstrahlung, electron capture bremsstrahlung, internal X-rays* and *external X-rays*. These five processes, of varying importance in the individual case, make up the entire photon production picture in the beta-excited source. These processes are reviewed briefly in the following paragraphs.

TABLE II

PHOTON PRODUCTION SYSTEMS

BREMSSTRAHLUNG
1. Internal Bremsstrahlung.
2. External Bremsstrahlung.
3. Electron-Capture Bremsstrahlung.
CHARACTERISTIC X-RAYS
4. Internal X-rays.
5. External X-rays.

Internal bremsstrahlung photons are produced at the parent nuclei concurrent with the change of nuclear charge which occurs upon the emission of the beta particle from the radioisotope. Internal bremsstrahlung has been shown to be independent of the Z number of the element by Stahel and Gullissen[4] and Wu[5]. Additionally, it makes up only a small fraction of the total bremsstrahlung. Bolgiano[6] has demonstrated that this electromagnetic radiation consisted of only $2.32 \cdot 10^{-3}$ mass units per beta disintegration for P^{32}, $1.9 \cdot 10^{-3}$ for Y^{91}, and $.84 \cdot 10^{-3}$ for radium-E; this being in agreement with theory. This photon flux is relatively unimportant in the beta-excited source.

External bremsstrahlung is that electromagnetic radiation produced concurrent with the deflection and accelleration of a beta particle as it passes through a nuclear field other than that of the parent atom. For thin targets, the energy of the external bremsstrahlung is proportional to Z^2 (atomic number of the target nuclei). The probability of emission of an external bremsstrahlung photon of a specific energy is proportional to the square of the target's Z number. The probability of external bremsstrahlung production decreases with the reciprocal of the photon energy[7]. External bremsstrahlung is the more important component of the total bremsstrahlung flux. In general, when a low energy source is desired (particularly true for the most energetic beta emitters), or when the characteristic radiation is the specific radiation required, then the external bremsstrahlung is that photon which must be minimized through design considerations.

Electron-capture bremsstrahlung is the counterpart of internal bremsstrahlung. This radiation is formed upon the nuclear capture of an atomic electron. Such photon production, again resulting from the change in the nuclear charge, is relatively small in magnitude. The frequency of this phenomena has been set at about 3.10^{-5} quanta per radioactive disintegration for Fe^{55}. Bradt[8] fixed this photon energy at about 70 Kev for this transition.

It might be of some significance to consider the relative fractions discussed above for the energetic P^{32} pure beta emission. Each P^{32} disintegration has assiciated with it; internal bremsstrahlung energy of 2.10^{-3} m_oc^2 units per transition and $8.2 \cdot 10^{-3}$ units of external bremsstrahlung, for aluminum target material, and about $56 \cdot 10^{-3}$ units of external bremsstrahlung for lead targets. This latter value illustrates the effect of increasing Z values on the energy dissipated in external bremsstrahlung per beta disintegration.

Internal X-rays are made up of those charactistic photons produced through ionization by the betas within the extended radioactive source itself. Such photon production is least important in the thin, carrier-free source and conversely is most apparent in the thick source. Carrier-free, source material will not show the effect as readily as the nuclide which is greatly diluted with its stable istopic component. In the latter case, the probability of ionization within the source is greatly enhanced by the presence of a large number of source atoms which, in this case, function as target nuclei (as in Figure #II). Beta emitters with a long half-life, such as Sr^{90} and Y^{90}, have been proposed as sources of characteristic internal X-radiation by this mode[9,10].

External X-rays are those characteristic photons emitted by external target atoms which are distinct from the beta emitting nuclei. These target atoms emit their characteristic X-ray photons in consequence of the ionization suffered from the beta particle impingement. External targets of A1, Sn, Ag, Cu and Pb, as well as some others, have been studied for the beta-excited effect[7, 11, 12]. Since we are concerned with work with the low energy, beta-excited source, the prime consideration is in the production of *external X-radiation* and of *external bremsstrahlung*. For the case of the low energy source, or for analysis or testing, the external X-radiation may be of first consideration. The external bremsstrahlung is important, for low energy work, in the sense that it introduces an unwanted high energy spectrum, which must be eliminated. Internal X-rays and internal bremsstrahlung are ordinarily not a desirable component of the X-ray flux. They may be important design considerations only in the sense that they are to be minimized, or eliminated. Internal bremsstrahlung, it has been pointed out earlier, is a rather unimportant component. Internal X-rays, on the other hand may make up a very significant portion of the total photon flux. Fortunately, they may be reduced by the use of proper design principles in the beta emitter itself.

RATIO OF CHARACTERISTIC TO 'WHITE' RADIATION:

The expression;

$$\frac{\left(\frac{dE}{dX}\right)_{(rad.)}}{\left(\frac{dE}{dX}\right)_{(ion.)}} = \frac{E\,Z}{800}$$

gives the electron energy loss per unit beta path length for bremsstrahlung (rad.), in ratio with the ionization (ion). E is the energy of the beta particle, in Mev, with which the electron enters the target. Z is the atomic number of the target material. This

is for monoenergetic electrons and does not strictly apply to the actual case where the betas exhibit a spectral characteristic. The expression shows that the ratio of bremsstrahlung to characteristic X-ray energy will be increased when the beta-ray energy, or the target Z, is increased. Usually, in the low energy source or for analysis applications, source design considerations are directed at the reduction of this ratio. The key to fabrication of the partical low energy, beta-excited X-ray source lies in the beta energies utilized, or more accurately, the spectral character of this particulate radiation, and in the ionization to bremsstrahlung ratios, which is obtained through the proper choice of source and target material.

Reiffel[13] has pointed up the paucity of data on efficiencies. Lebeouf and Stark[11] have shown the efficiencies in Table III. For characteristic tin X-rays, they obtained efficiency values of about 1% for S^{90} — Y^{90} source betas, and about .3% for the less energetic Pm^{147} betas. 6% and .3%, respectively, were found for tin targets for *external bremsstrahlung,* for the same radiation. The change of efficiency with change in beta energy is significant. Efficiency values as high as 10% have been given by Reiffel[13] for lead targets. These efficiencies are in terms of photons produced per unit beta particle which is incident upon the target material. Sr^{90} — Y^{90} and radium-E have efficiencies of 10^{-3} to 10^{-4} for internal X-ray production (Reynard[10]). The 'white spectra' from the tin target will mask the external X-ray production with the energetic Sr^{90} — Y^{90} source.

TABLE III
BETA-EXCITED SOURCE EFFICIENCY
IN PHOTONS/INCIDENT BETA*

Energy	K X-ray**	Source	Bremsstrahlung
Sr^{90} — Y^{90}	2.2 MEV	$1x10^{-2}$	$5x10^{-2}$
Pm^{147}	.22	$3x10^{-3}$	$3x10^{-3}$

**L and M X-rays may also be present.
*Leboeuf and Stark[11], (for Sn target).

APPLICABLE RADIOISOTOPES:

It is obvious from the review of the action of the thulium source that the radionuclide must be a pure beta emitter. The A. E. C. catalog, of pile irradiations, lists almost 100 routinely available nuclides. It is a serious hinderance to the designer of the beta excited source that only a minor fraction of these are pure beta emitters. The balance being made up almost entirely of combined beta-gamma emitters. The gamma radiation from these radioactive isotopes usually is of such an energy and intensity to mask the function of the beta-source. Table IV lists the characteristics of some of these isotopes which emit gamma rays. The photon energy ranges from .7 to 3.8 Mev. Where the nuclide is also a beta emitter, this high photon energy obviates the use of the nuclide in a beta-excited source, particularly for applications below 100 Kev.

Slightly less than 20% of the isotopes routinely produced in the Oak Ridge pile are useful pure beta emitters (for application to the beta source). Table V lists fourteen of these. The maximum spectral energies range from 18 Kev to 2.2 Mev. Sr^{90}, Y^{90}, P^{32}, Pm^{147}, Ca^{45} and W^{185} have been studied for their potential in the beta-

TABLE IV
GAMMA EMITTING, PILE PRODUCED RADIOSOTOPES*

Radionuclide	Half-Life**	Gamma Energy*** (Mev)
Sodium-24	15.06 h	2.754 #
Gallium-72	14.3 h	2.51 #
Lanthanum-104	40 h	2.50 #
Iridium-194	19 h	2.1 #
Antimony-124	60 d	2.04 #
Arsenic-76	26.8 h	1.7 #
Praseodymium-142	19.2 h	1.59 #
Silver-110m	270 d	1.516 #
Potassium-42	12.44 h	1.51 #
Europium-152, -154	12 y; 16 y	1.40 #
Cobalt-60	5.27 y	1.33 #
Bromine-82	35.87 h	1.312 #
Iron-59	45.1 d	1.289 #
Tantalum-182	115 d	1.223 #
Scandium-46	85 d	1.12 #
Zinc-65	250 d	1.12 #
Rubidium-86	19.5 d	1.08 #
Rhodium-106 (Ru^{106})	30 s	1.045 #
Cesium-134	2.3 y	0.794 #
Tungsten-187	24.1 h	0.78 #
Zirconium-95	65 d	0.754 #
Niobium-95	35 d	0.745 #
Barium-137m (Cs^{137})	2.6 m	0.662

*U.S.A.E.C. Catalog of Radioisotopes.
**h, hour; d, day; y, year; m, minute; s, second.
***The energy given in each case is the maximum gamma energy which occurs in 5% or more of the radioactive transitions.
#Also a beta emitter.

excited X-ray source[7,14]. Not all pure beta emitters are useful in the beta-excitation mechanism. Design and fabrication limitations may be imposed by; one, *the available form* (chemical and physical), in which the isotope may be irradiated; two, the *half-life*, which, when short, limits the isotope's usefulness to experiment only; three, *the specific activity*, which will fix the output intensity and indirectly influence design efficiency and the minimum source volume available (this latter is a critical factor since it fixes the minimum exposure times in analysis or radiography); four, *the maximum particulate energy*, which will influence the photon production efficiency and the

$$\frac{dE/dX\ (rad.)}{dE/dX\ (ion.)}\ \text{ratio.}$$

Several of the isotopes in Table V are ruled out for use in the *low energy source* due to the high maximum energy of the beta spectra. Some of the materials are available as carrier-free elements. Use in this form will provide the greatest concentra-

TABLE V

PILE-PRODUCED PURE BETA EMITTERS*

T½**	Radioisotope	Maximum Energy (Mev)
2.54 D	Yttrium —90	2.18
13.7 D	Praseodymium —143	0.932
14.3 D	Phosphorus —32	1.701
53 D	Strontium —89	1.463
73.2 D	Tungsten —185	0.428
87.1 D	Sulfur —35	O.167
163 D	Calcium —45	0.254
2.6 Y	Promethium —147	0.223
12.4 Y	Hydrogen —3	0.01795
25 Y	Strontium —90	0.61
85 Y	Nickel —63	0.067
5568 Y	Carbon —14	0.155
2.12×10^5 Y	Technetium —99	0.29
3.08×10^5 Y	Chlorine —36	0.714

*U.S.A.E.C. Catalog of Radioisotopes.
**D, day; H, hour; Y, year.

tion of betas per unit source volume and will fix self absorption at a minimum value for a given activity. Approximation to a point source may be a critical design factor in the beta-excited source fabrication. This may be especially important for certain usages in radiography. A true point source obviously cannot be realized physically but an attempt to approach this end may be necessary to design the particulate source (beta) into the smallest possible volume, without sacrificing the source intensity. The smallest volume ultimately obtainable is controlled by the highest specific activity of the beta emitter which is chosen. This, in turn, will be controlled by pile characteristics, half-life, age and the chemical and physical forms available. Table VI gives the spherical volume into which one curie of beta emitter, with an arbitrary density of five, may be packed; assuming that carrier-free material is available. The radius of the beta source would be only 170 microns for the tungsten sphere. It should be

TABLE VI

SPHERICAL VOLUME OCCUPIED BY ONE CURIE OF CARRIER FREE MATERIAL*

Isotope	Volume	Radius in Centimeters
W^{185}	2.1×10^{-5}	1.71×10^{-2}
T^{170}	3.1×10^{-5}	1.95×10^{-2}
Co^{45}	1.0×10^{-6}	$.62 \times 10^{-2}$
Pm^{147}	1.9×10^{-4}	3.57×10^{-2}
Tl^{204}	3.1×10^{-4}	4.20×10^{-2}
Sr^{90}	1×10^{-3}	6.2×10^{-2}
Sr^{90} - Y^{90}	5×10^{-4}	4.93×10^{-2}

*Assuming an arbitrary density of 5. Some of these isotopes are not routinely available in carrier-free form. They are shown only as examples.

pointed out that W^{185} is not routinely available in the carrier-free form, and is used here only for an example. However, this isotope, if available as carrier-free material would have associated with it; 9.660 curies per gram. For Ca^{45} the specific activity would be about 20,000 curies per gram. We must review, at this point, the fact that we are speaking only of the beta emitting nuclide and its associated physical dimension. The dimensions of the *assembled beta-excited photon source* are fixed by the beta range in the target, plus other considerations. These dimensions, with the proper source design, therefore, can be made quite small. Source dimensions approximating those in the Coolidge X-ray tube are feasible. P^{32}, Pr^{143}, Sr^{89}, S^{35}, Ca^{45}, Pm^{147}, H^3, Sr^{90}, Y^{90}, C^{14} and Tc^{99}, (all pure beta emitters) may be obtained in the carrier-free form or in a special *very high specific activity form.*

PHYSICIAN DESIGN:

The components of the beta-excited source fall into two main units. The first is the *isotopic source of betas.* The second is the *target material.* These two may be fabricated and arranged in juxtaposition in many physical, chemical and geometrical forms and combinations. However, in the following paragraphs, the more simple classical designs of target geometry will be reviewed. Targets fall into the three general categories listed blow:

(A) *Transmission* target type.

(B) *Reflection* target type.

(C) *Fluorescence* target type.

The *transmission* or 'casing' target is one in which the coherent, combined beta paths, up to the point of origin of the X-ray photon, plus the resultant photon path, traverses the target volume from side to side. The *reflection* target functions in a manner analogous to the target in the conventional X-ray tube. In the reflection type, the trajectory of the incident beta plus the path of the resulting photon occupy the volume on only one side of the target plane. The *fluroescence* target is one in which the characteristic target X-rays are induced by beta-excited photons from a second target (this latter target usually being intimately designed with the beta source). It is obvious that a single target may experience one, or all, or combinations of these functions. Generally however, the target design and orientation will provide for *one primary function.* The three types of target design are shown in Figure #3. Figure #3a schematically illustrates the transmission target which is shown as the volume TT. This is placed in proximity to the radioactive source S. The beta particles which are designated as the straight arrows impinge upon TT and the X-ray photons (B and CX), which are produced, traverse TT and exit from its other surface. The *backing target* BT is often used in this geometry to improve the efficiency. The 'sandwich' which is illustrated is made up of only one transmission target. BT is a reflection target which is useful in this binary target design. This laminated source design is quite applicable to the fabrication of a planar source design and will be treated later in detail. The transmission target TT must be at least as thick as the maximum range of the source betas so that none of the particulate radiation may escape by passing entirely through TT. Added target thickness however will serve only to harden (through self-absorption) the X-ray spectrum emerging from the right side of TT. This is undesirable. Figure #3b illustrates a technique which makes possible the use

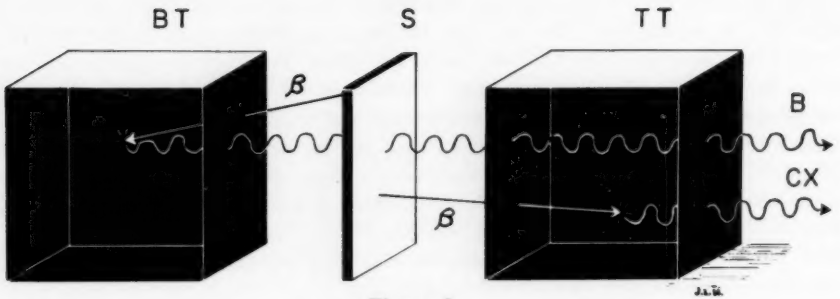

Figure 3a

TT is a transmission type target for the beta-excited source. Beta radiation from S (straight arrows) are absorbed in TT. The resultant ionization process produces the characteristic X-rays CX. Bremsstrahlung may result from the beta interaction with the backing target BT. This target utilizes the reflection mode (see text). The sandwich design with BT, S and TT is used to increase source efficiency.

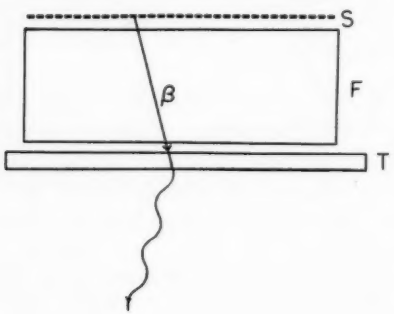

Figure 3b

A low Z number absorber F is interposed between the source S and the target T. Proper choice of thickness of F will reduce the energy of the betas impinging upon T and will allow use of a thinner target. The bremsstrahlung to ionization ratio may be reduced by this technique.

of transmission targets which are thinner than the maximum range for that material. The source S at the top has a layer of low Z material (F) such as lucite placed below it. On the bottom of this is the transmission target T. In this case, beta radiation from S expends some of the energy in F before reaching T. The beta's total energy on reaching the top surface of T is now much reduced from that extant when it left the surface of S. This means that the $\frac{E\ Z}{800}$ ratio (equation #I) is now reduced (in favor of the ionization process). The use of a thinner transmission target T may be desirable but this technique can have some pitfalls. Improper choice of absorber thickness F disproportionately extracts only the low energies from the radionuclide's beta spectrum and may leave the more energetic side only slightly affected. This is possible because we are dealing with a spectral character. This will then mean a greater bremsstrahlung to X-ray ratio. Thus, the beta spectrum shape and the maximum beta energies must be taken into account when using this system. The absorber method radically reduces efficiency of the source mechanism by extracting betas from the total flux which ordinarily would impinge upon the target, and for this reason is ordinarily not used.

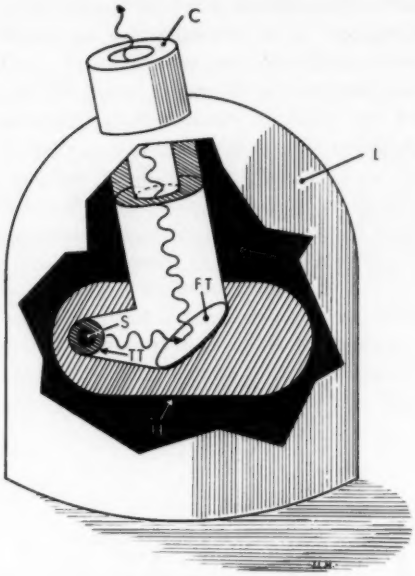

Figure 4a

This is an example of a fluorescence target design. The fluorescence target FT is mounted in proximity to a casing target TT which surrounds the intense beta emitter S, which here is in the shape of a sphere. The inherent inefficiency requires that good geometry and a small, intense beta source be used. This in turn will require heavy shielding at H, L and C.

Figure #4a is a schematic illustration of a beta-excited fluorescence target type. This is a cross section through the source and its associated radiation shielding. The beta emitter is in the form of a tiny sphere of carrier-free material, and is designated by S in the sketch. The casing or transmission target TT is fabricated as a shell completely surrounding the sphere S and of maximum range thickness. The fluorescence target FT is exposed to the bremsstrahlung and X-rays which are produced in TT (wavy line). S and TT can be imbedded in a collimator or gun which is directed at FT. Those photons which impinge upon FT may produce an appreciable amount of characteristic or fluorescence radiation, providing that the variables of self absorption and resonance are properly oriented. The characteristic resulting photons may be passed throught a system of collimators, C. The Source S in such a design must be very intense. Therefore, it may be wise to house this in some dense shielding, H, such as hevimet. This will serve to stop that random radiation which is not directed at FT. The collimator (C) may also be made of hevimet. The whole may be housed in a lead shield of spherical or semi-spherical design. The source efficiency of such a system is very low; probably being of the order of 10^{-3} fluorescence photons per beta disintegration. This is for the case of best geometry. In the practical case the efficiency would be 10^{-1} to 10^{-2} below this. The advantage of this system is that it can produce essentially monochromatic X-radiation. It has certain potential in analysis and particularly for calibration work.

Figure #4b shows a hypothetical reflection target design in cross-section. The intense sphere of beta emitter, S, is embedded near the center of the lead shielding sphere L. The particulate beta radiation, straight arrows, strike the reflection target RT. Some of the beta particles are reflected or scattered from the surface into the volume of the aperture, but these are absorbed by a thin window of low Z material, such as lucite, which is shown here as F. Other beta particles which impinge upon RT interact with the target material and bremsstrahlung and X-rays are produced. This electromagnetic energy may be propagated in all directions. That which passes through the aperture volume may be utilized for radiology or radiography. The filter F will present little obstacle to the photon (curved arrow). The reflection target type is less efficient by a factor of ten than the transmission type but it is highly useful where the photon absorption in the target material is high, or where very low energy betas must be used with a very thick target. Target mixtures, such as lead-barium, have been proposed for a greater spread in photon energies. Targets which are fabricated at an atomic or molecular level with the source will be discussed in the following section.

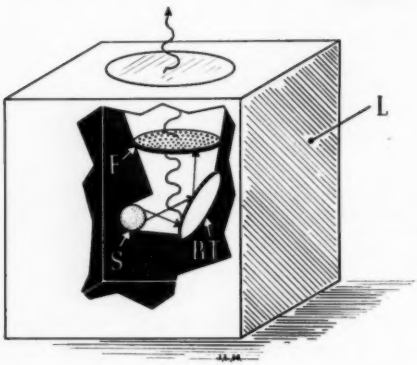

Figure 4b

The reflection target RT is embedded in a lead shield L near the intense beta source S, in this schematized cross section of the reflection target system. The low Z filter F absorbs the betas which are scattered from RT. Photons (curved arrow) pass the filter and are collected outside the shield. This is a less efficient technic than the transmission target. This model of a beta-excited source type has its almost exact counterpart in the conventional X-ray tube.

Although the target type is of some importance, the relative orientation of both target and the beta source is also of considerable importance. Table VII lists these possible orientations as; separate, intimate, mixture, compound and elemental. The photon production efficiency, which is of prime importance, is especially dependent

TABLE VII

RELATIVE SOURCE-TARGET GEOMETRY

1. Separate Source-targets.
2. Intimate Source-targets.
3. Mixture Source-targets.
4. Compound Source-targets.
5. Elemental Source-targets.

upon the relative juxtaposition of beta source and target. Figure #5a gives an example of source and target volume arranged in separate geometry, (A). Obviously, this

is the least efficient positioning because of the beta losses imposed by the inverse square law. The greater the separation, the lower the efficiency. However, such separation is often necessary because of a need for collimators between S and T. B in Figure #5a is the same source, S, and target T in intimate *geometary*. This is obviously a much more efficient geometrical design than A.

In C the 'sandwich' of backing target, BT, source S, and transmission target T is shown. This is a reasonably efficient design and is discussed in the following text. An obvious extension of the sandwich design is the shell or casing target in intimate contact with a small sphere of the beta emitter. This latter source-target geometry is highly efficient when the beta source sphere has negligible self absorption.

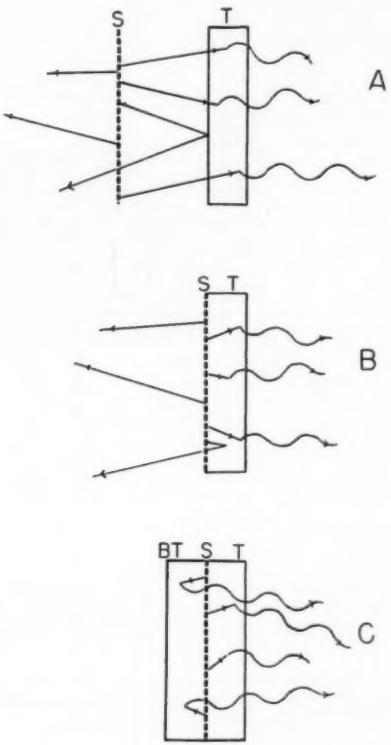

Figure 5a

A, B and C represent respectively examples of *separate, intimate* and *'laminar'* or *'sandwich'* source-target geometries (top to bottom).

It is apparent, from the point of view of geometry, that greater efficiency can be expected from the geometries in which the source is more intimately packed with the target material. This may be extended to the logical conclusion that positioning on the macro, micro and atomic scale should produce progressively better photon production efficiencies. Figure #5B presents in idealized form the source target geometry representing a source-target *mixture* design, M, on the left, and the *compound* design, C, on the right. In each case, the beta emitting radionuclide is represented by the small x's and the target atoms as the solid dots. When the beta-source material

and the target are mechanically mixed, the rather irregular, but close, disposition of the two components in M will be achieved. In actual practice this irregular orientation will not be on the atomic level as shown; but rather, each component will exist in small clumps or crystallites with irregular spacings between these groups. The source and target, in M, may be mechanically mixed as a complex powder, slurry, amalgam or liquid suspension. One might precipitate two separate compounds simultaneously and pack the damp mixture together and then allow to dry. In general, this method of mixtures should reduce losses due to beta source absorption and to the inverse square law, and will result in an improved photon production efficiency. Another method, which is illustrated under C, provides for a more intimate and regular positioning of the target and source. This is accomplished by introducing the source atom

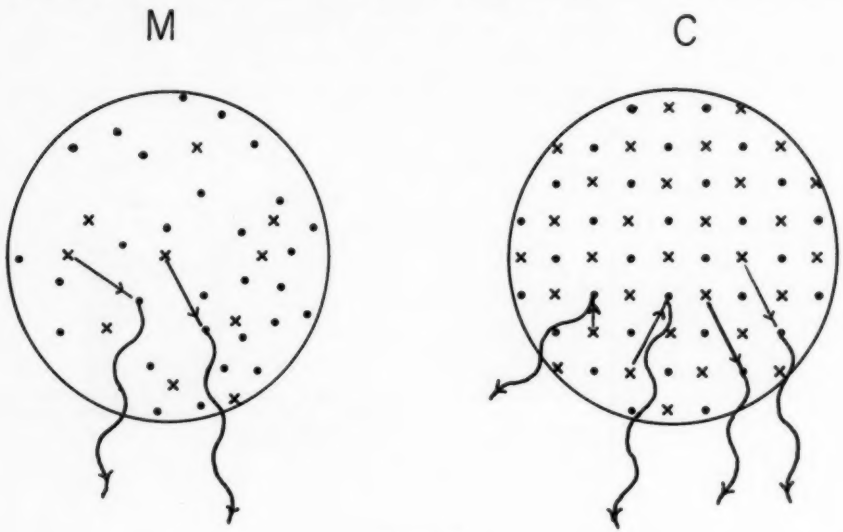

Figure 5b

M represents the *mixture method* of positioning target material near the beta source. This might be as a powder, slurry, suspension, colloid, etc. The small x's represent the isotopic beta emitters. The dots are the aggregates of target atoms. Note that the beta sources would be expected to be irregularly spaced.

C represents the *compound source-target geometry*, with the radioactive atoms (x) and the target atoms (dots) arranged in a crystal lattice. This very close positioning of the beta source and target atom can greatly improve the likelihood of an interaction between beta and target atoms.

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and the target atom or atoms into the same chemical compound. This compound may be in the form of small or gross crystallites, but it is preferable that the whole mass be grown as a single crystal. In such a model, it is possible to surround each radionuclide with several target atoms, as shown in Figure #5B. Very uniform and intimate positioning is possible by this method. The probability of interaction between the beta particle and the target atom is enhanced since the separations are only of the order of atomic dimensions. The compound and mixture source-target arrangements have the advantage of containing the source within small dimensions and of packing the two

components in a very intimate array. It might be pointed out that solutions of beta-source and target material will also establish the uniform and close mixing seen in C. It is difficult to categorize this target type for M or C, since it may have a different function at its periphery. However, it may be classed as an adaptation of the transmission target. It is obvious that the betas which originate near the surface of such a source may escape into the space outside the source, thus causing a beta exposure problem and a health hazard. Figure #5C shows such a source packed into a spherical void in the center of a spherical filter of low Z. The betas expend their energy in this filter, whereas the electromagnetic radiation passes with negligible absorption.

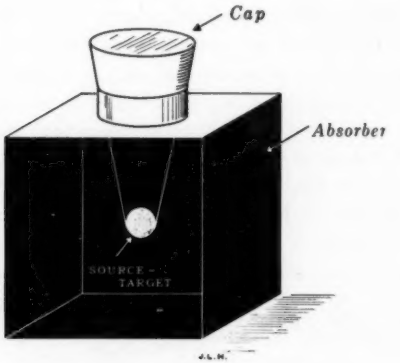

Figure 5c

The small spherical *mixture* or *compound* source-target arrangement (cross-hatch) may be sealed into a spherical, or cubical, lucite shield, as shown, so that betas escaping from the periphery of the source are stopped by the surrounding low-Z filter material.

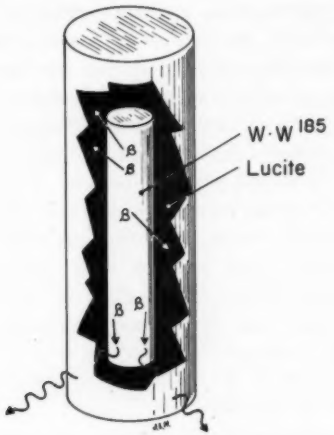

Figure 6

This is the elemental source-target geometry in which irradiated W^{185} are incorporated into the W wire crystal structure. Betas from the W^{185} utilize the surrounding tungsten atoms as a target array. Lucite absorbs the peripheral betas.

Possibly the most intriguing source type is the *elemental source-target* design. Figure #6 is an idealized sketch of this. This source type has this beta source element and the target element all in a single physical form, and this in a closely packed crystal structure. This unique advantages of this technique are obvious. Some of the disadvantages are not as clear but will be dealt with in the following. The center rectangle, in Figure #6, represents a small diameter pure tungsten rod which has been irradiated in the neutron flux of the Oak Ridge Pile. Its specific activity is about 100 millicuries per gram of W. The W^{185} beta radiation from this pure emitter will use the surrounding tungsten atoms, within the metal crystal, as target material. Internal and external bremsstrahlung will result, as well as the characteristic X-radiation of tungsten. The low Z filter which encases the metal will absorb the peripheral escaping betas. An obvious advantage is the possibility of prefabrication of complex designs in the metal before irradiation. The source-type is not without its problems. The source may have an extremely high absorption coefficient for its charactistic X-rays. It may be limited to relatively small sources, or thin sections of metal, since it may exhibit

considerable self absorption for the characteristic or the entire photon spectrum. This would be especially true of a dense metal tungsten source.

The activated beta-excited source is another physical form which affords some unique potential. This involves pile neutron activation of the entire beta-excited source and as a consequence requires some special characteristics. This system will be termed hereinafter, the *'compound source-target activation process'*. Ordinarily the creation of the beta emitter takes place either by a neutron irradiation process in the pile or through the phenomena of fission. I^{131} and Sr^{90} are products of the latter process. W^{185} is a product of the neutron irradiation system. Ordinarily the beta emitter (either non-processed or prefabricated) is created separately from the target material by pile irradiation. *Separate beta source activation* refers to the insertion, alone, of this beta source material, into the pile for activation. The radio-active nuclide, thus produced, is then used 'as is' or processed for insertion into the beta-excited source. This more conventional method allows fabrication to take place *only before* the irradiation. Post-irradiation fabrication of the very intense beta sources is not practical due to the severe health-physics hazards. *Compound source-target activation* refers to the simultaneous exposure to the pile's neutron flux or both the target and the beta source material. This is done with the entire source in its final assembled form. This special design is quite practical where the target material is relatively short lived. A good example would be for the case of iodine incorporated as target material. I^{128}, with its short half life, makes it practical to incorporate calcium as a stable calcium ion into a calcium iodide crystal and to place this for neutron activation into the pile. The neutron flux will produce, of course, a tag in which the iodide compound will have incorporated Ca^{45} and I^{128} in its structure. The very short-lived I^{128} will decay to negligible proportions leaving the stable iodine, plus the longer lived Ca^{45}. The Ca^{45} will serve as a pure beta source and the I^{127} the target material. The advantage here is that the extremely hot source needs no special post-irradiation fabrication or fitting to the target following irradiation. This greatly minimizes the problem of personnel exposure and the necessity for difficult remote control operations and facilities. The relative neutron cross sections for the two elements in the compound are important. Obviously, if the short lived material has a cross section 10^6 times greater than that of the pure beta emitter; then the source may be useless for a very great length of time following irradiation. Coleman[7] has suggested the use of multiple radioactive sources to obtain the proper beta spectrum.

Requisites for irradiation and shielding must be considered prior to insertion of a source component into the pile. Some of these criteria are listed in the following:

1. Physical size.
2. Purity.
3. Source stability.
4. Radiocontaminants present (due to trace impurities or daughter products).

PART 2

The following section covers the experimentation with specific beta-excited X-ray sources. The isotopes which will be discussed were often purposely chosen because of their short half lives. This simplified the disposal and waste hazards.

Additionally, the quantities used were of relatively low total activity. Total amounts used in the individual sources were of the order of one millicurie. The low activities used were practical since these sources were designed for strictly experimental purposes. The exposure times which were used could be, as a consequence, quite long. The lower activities, utilized here, enabled the workers to carry out routine manipulations without complex procedures imposed by health physics hazards. Additionally, exposure time was not a critical factor as it would be in radiology, radiography or surface therapy.

Activity levels for the practical beta excited source would probably begin in the 10^2 mc range, or above, and would extend well into the multicurie level. Rather massive and complex shielding may be necessary in such very high-activity practical sources. This has been a major disadvantage to the high level beta sources[13]. Important criteria to consider in shielding design are as listed; the minimum shielding allowable (from a tolerance dose standpoint; bremsstrahlung production in the shielding material; characteristic external radiation from the high Z shield; fluorescence from the shield; and advisability of the use of low Z primary and a high Z secondary shield lamination.

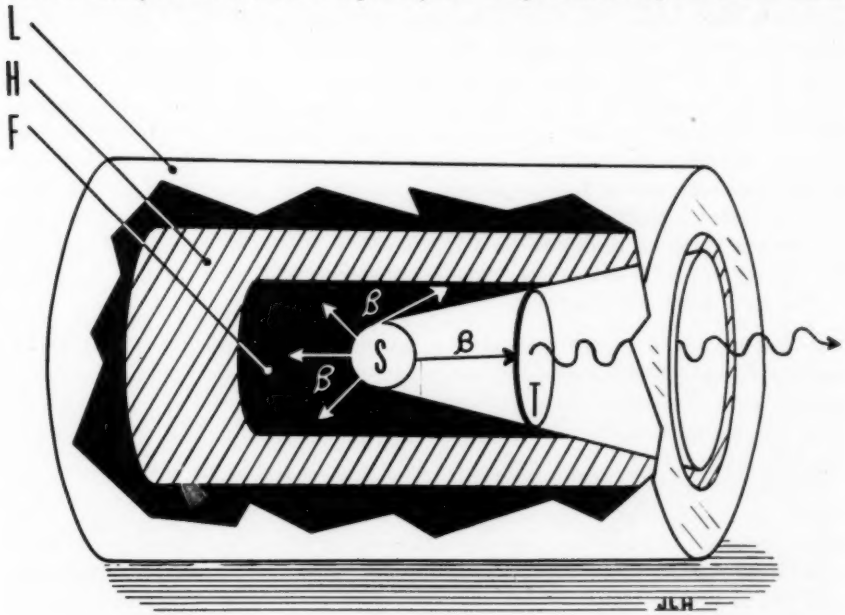

Figure 7

This schematic illustration of the use of a primary and secondary shield for the beta source. The low Z shield F absorbs the betas directed at the lead shield. This reduces the probability of production of undesirable bremsstrahlung photons in the shield.

Figure 7 illustrates the use of low Z filter F (lucite) near the source S to absorb those betas not directed at the target and composed of a material which will not produce bremsstrahlung or energetic external X-rays. The use of the low Z absorber near the beta emitter may actually make the shield less bulky by eliminating the

greater portion of the beta induced, high energy, photon production within the shield which immediately surrounds the source. The function of the rest of the shield will be confined only to absorption of back-scattered electromagnetic radiation from the target and from that photon production which takes place in the source itself.

THE APPOSITION SOURCE:

The initial research into this source type at this laboratory developed through an investigation of a low energy X-ray source of planar design with a required dimension of about 2 centimeters diameter. This was to have some applications in gross apposition microradiography and autoradiography. Very thin uniform layers of Cr^{51} produced by vacuum evaporation had been studied for this purpose when construction of the planar beta-excited source was initiated, Figure #8. This is an application of the sandwich design which was described earlier, in which the source is in laminar form between the two layers of target material. The beta ray source, S, of P^{32} (carrier-free; as the phosphate), Sr^{90}—Y^{90} or Pm^{147} may be plated either on the transmission target TT or on the backing target BT. H is a brass assembly sleeve. L is the source's cylindrical brass body. This design constitutes an attempt to provide a uniform, planar source of X-rays from the copper targets. Targets thickness is chosen for maximum range for the maximum energy beta of the particular istope utilized. Figure #9 is a view of the disassembled source. The device is roughly one inch in diameter and one inch tall. The source intensities were of the order of one millicurie of pure beta emitter. No extra shielding was used for the experimental work done with this source. Deposition of the pure beta emitter from a solution in the form of a phosphate as a uniform layer presented a problem difficult of solution. The uniform deposit was secured by a technique involving deposition on a thin layer of paper and subsequent cutting of the deposit area to fit the source. This technique results in very uniform distribution of the dried down material.*

The diminutive size of the source is graphically represented in Figure #9. In order to increase the intensity over that used in the experimental studies, it would be necessary to incorporate some shielding about the cylinder shown in Figure #9. Even so, the entire source (shield plus source and target) could be kept in a sphere less than 4" in radius. This is still a great deal less than the required space for the conventional X-ray circuitry. The planar source was to be used for gross apposition studies, as in Figure #10. The laminated source is placed in apposition with a very small subject P, which in turn is positioned on the autoradiographic emulsion E. Resolution of the system was of some importance and some investigations were carried out with this general configuration. For best resolution, the ideal impingement angle with the emulsion for the X-ray photons, formed in the target material BT and TT, is at 90° to the emulsion surface. This target design provided photons which strike the emulsion surfaces at all angles. Important factors here will be the thickness of the emulsion, the subject's length and the gross dimension of the source. The resolution will be better when the emulsion is thin and the subject is large relative to the emulsion thickness. The separation between source and emulsion surfaces will also be of some importance. Resolution studies were carried out by the device in Figure #9 and in the geometry as shown in Figure #10. Generally the subject thickness was of the same

*Paper in preparation.

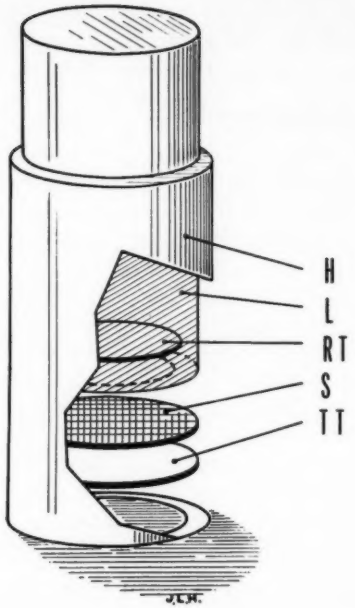

Figure 8

The planar, apposition, beta-excited X-ray source is schematized in cross-section. This was designed for gross apposition microradiography. Constructed on a laminar target design, TT and RT are the transmission and reflection targets respectively. S is the beta source (Figure 7).

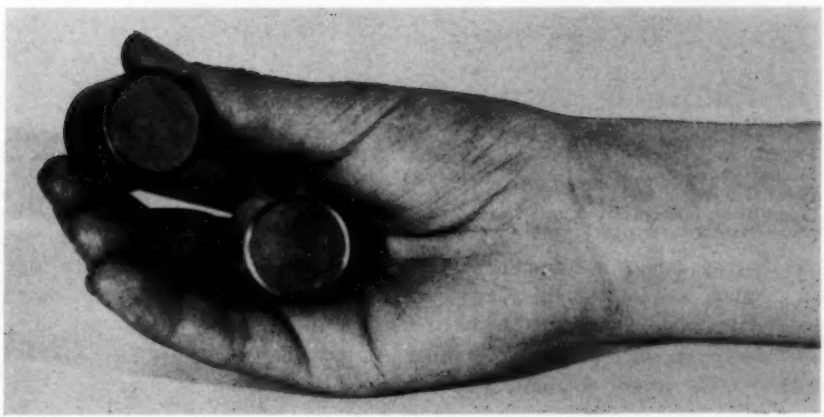

Figure 9

The small size of the disassembled, planar beta-excited photon source is shown here.

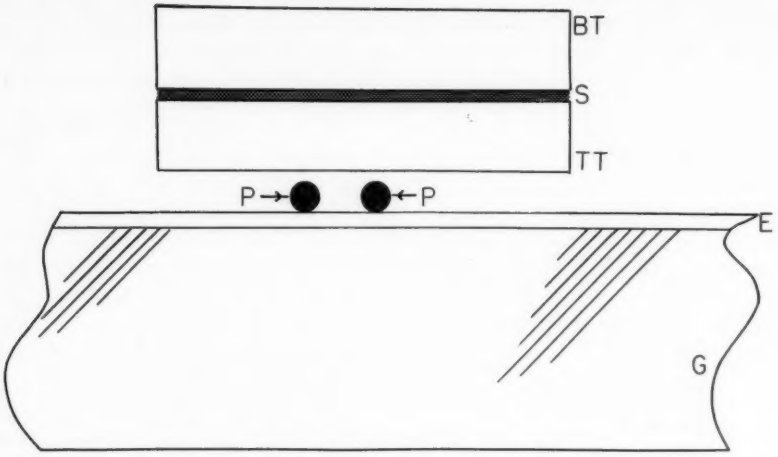

Figure 10

Gross apposition set up for planar beta-excited X-ray source. BT and TT are backing and trans. mission targets respectively. S is the radioactive source. P represents the macrostructure under investigation. E is the photographic emulsion and G the backing.

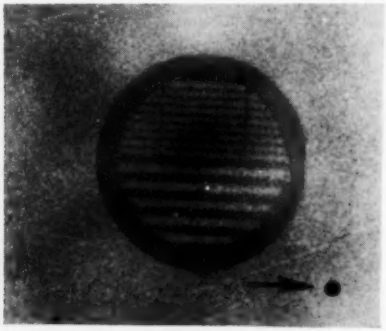

Figure 11a

This is an apposition exposure with the beta-excited source outlined in Figure 7. The subject is a copper screen one mil thick. The copper disk is about 3 mm in diameter. (See the silhouette lower right, arrow,)

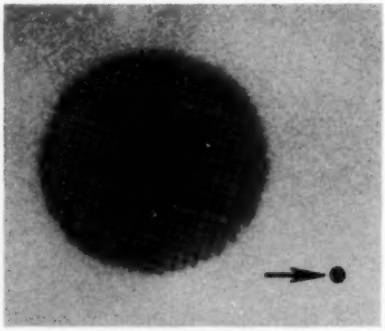

Figure 11b

A 200 mesh nickel screen was used here with the copper sandwich source in Figure 7. Structures which are resolved are grossly of the order of 50 microns in size. (The disk's size is shown at the arrow).

order of magnitude as the emulsion thickness and the separation between the source and emulsion was also of this order of magnitude. However, the gross dimensions of the subject, (length and breadth) were large relative to the emulsion thickness.

Figure #11a shows the resolution obtained in a study in which the subject consisted of a thin copper disk about .005" thick and about 2 mm in diameter.

This resolution study with this patterned copper foil shows a resolution which is of the order of 75 microns. The resolution of the very thin segments of this grid illustrate the presence of some low energy radiation from this beta-excited source. Figure #11b is another apposition exposure made with a 200 mesh nickel screen which

was ⅛" in diameter. A beta source, consisting of about one millicurie of P^{32}, in solution as the phosphate, was dried down on a special, thin, paper lamination, sandwiched between the two targets BT and TT in Figure #8. The apposition exposure was for 1.5 hours on Kodak medium lantern slide emulsion and development was in Dektol for 3 minutes. Resolution shown by this exposure is of the order of 50 microns. Extension of these resolution studies below this level was difficult, due to the problem of finite grain size in the m.l.s. emulsion. The variations in background density are due to unequal beta emitter surface concentration. Most deposition concentrations were less than 1 mg per sq cm. The contrast available here demonstrates that some low energy radiation is available from the spectrum of this source despite the high maximum energy of the betas. As is the case with most apposition work, the quality of the images depend largely upon the excellence of contact between the emulsion, subject and the source of radiation. Where the contact is quite perfect resolution of the order of 25 microns seems possible even for very thin specimens.

The apposition source which is described here was designed entirely for experimental purposes and was charged with a low-level beta source. Such a source could be increased in activity many fold. Where exposure times are unimportant, or where the source can be fixed to the subject for rather lengthy periods, therapy dosages may be administered to the surface layers from such a source. This has no immediate application for human usage but may have some usefulness in animal experimentation. An interesting facet of this apposition design is that it may be constructed to fit

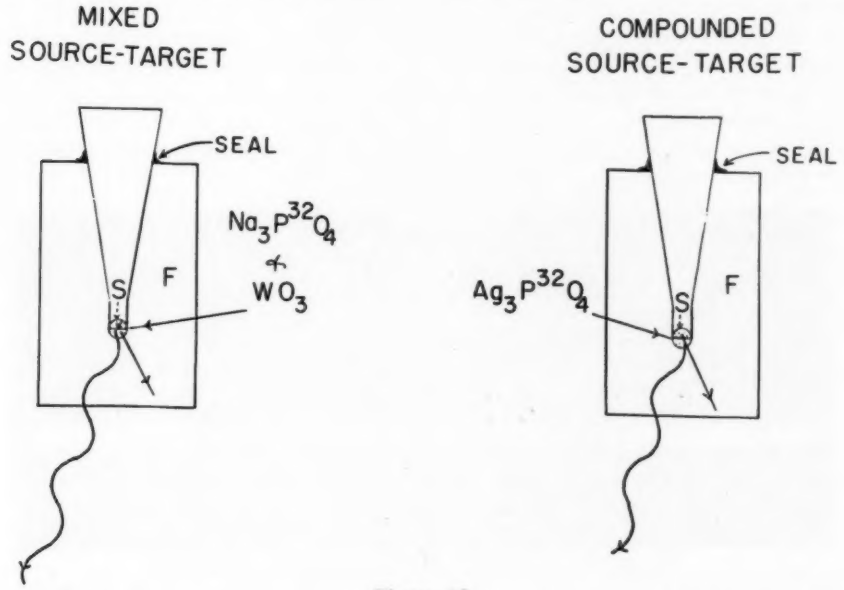

Figure 12

The beta-excited source types are illustrated in schematic form. The mixture of $Na_3P^{32}O_4$ and WO_3 as powders on the left illustrate a 'miture source'. P^{32} serves as the beta source, tungsten as the target. The 'compound source' on the right is made up with the target silver and radioactive P^{32} incorporated into the same molecule. The diameter of these packed sources may be two to three millimeters. This will give good resolution when subjects and sources are separated by about 20 cm.

any type of complex surface. Thus, it might be fabricated to fit a certain portion of the skull of an animal for surface therapy studies.

In addition to the apposition source above, some exposures were carried out with both the *mixed* and the *compounded* source-target geometries, which were described earlier. Figure #12 is a schematic of the devices which were used for this. The mixture type shown on the left in Figure #9 may consist of any two distinct materials (they may be elemental, or chemical compounds) usually in a powder form. One material incorporates the isotopic beta emitter and the other contains the target material. These materials may be mixed in a variety of techniques as described earlier. However, the intimacy of mixing cannot exceed by much the macro-scale. A technique, evolved here, consists of the precipitation of the two materials and packing of the still damp compounds into the lucite body. This obviates certain problems of health-physics associated with the dried powders. P^{32}, in the phosphate, serving as the beta source, and tungsten introduced into the mixture as the oxide are examples of the mixed source-target in Figure #9.

The compound which contains both the beta source and the target atom is a more efficient means of beta-excitation and is shown on the right in Figure #9. Silver phosphate contains both source and target atoms and when grown as a single crystal gives uniform geometry at separations of the atomic dimension. For the example given, each P^{32} atom will be accompanied in the crystal lattice by three target atoms of silver. This latter design was utilized, but facilities were not available at this laboratory for growing of radioactive single crystals. The compound (Ag_3PO_4) was packed in the receptacle in the lucite housing. The volume in which this source is packed may be made quite small. By mounting the source at a distance from the object and the X-ray emulsion, this small size maybe utilized to produce good resolution of relatively small objects. The dimension of this source type approximates the focal spot size of some X-ray tubes used for radiology. For the 3 mm source, resolution of 100-200 microns was anticipated.

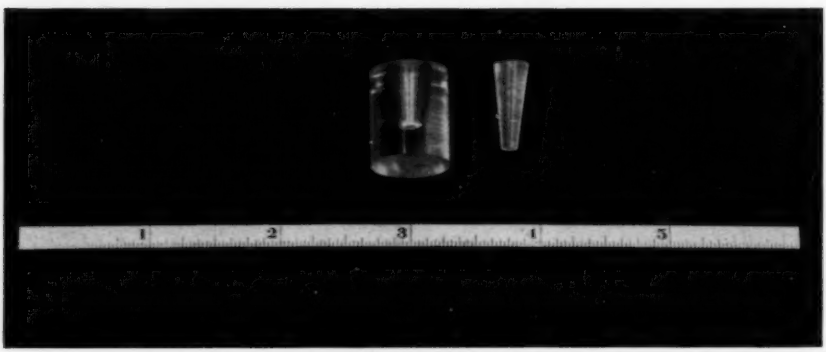

Figure 13

The disassembled lucite housing for the compound beta source. The void for the compound is cylindrical in shape.

The disassembled lucite body is shown in Figure #13. The cavity in this case is cylindrical in shape and about 3 mm in diameter and 3 mm high. This source type

suffers from a lack of intensity, but if this disadvantage can be obviated, this compact resolution source could be a competitor with conventional X-ray devices for use in the field. The lucite housing is about one inch tall by 1" in diameter.

The quality of X-ray production by this source was evaluated grossly here by radiography of miniature electronic tubes. Brownell[14] has used phantoms consisting of paraffin embedded with materials of various density to evalute the radiological quality of such sources. Figure #14 is a reproduction of a radiographic exposure of a miniature electronic tube. The beta-excited source was of the compounded type. It consisted of a 3 mm diameter silver phosphate source. The beta activity was 2.4 millicuries. This was mounted in a lucite housing similar to the one in Figure #13. The phosphate was packed into the void and sealed in with a clear lucite solvent (ether). This results in a relatively clean lucite source from a health-physics viewpoint. The subject was positioned on a special casette*. The source was rigidly suspended above the casette at a distance of 20 cm. The source was 50 to 75 milligrams. The exposure was for about 100 hours on special Kodak X-ray *Royal Blue emulsion* which carried the designation *SO-1197*. *Dupont Lightening Intensifiers* were used. The fine structure of the tube is moderately well delineated. Some of the leads which are

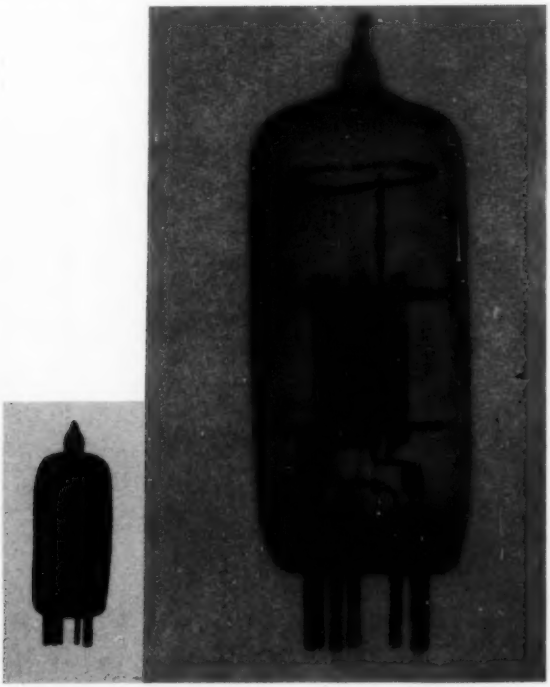

Figure 14a

Exposure of a miniature electronic tube by a 3 mm spherical silver phosphate source oriented at 20 cm from the subject. Some wires 5 mils in diameter are well resolved. Relative size of subject is shown in silhouette at left..

*To be reported.

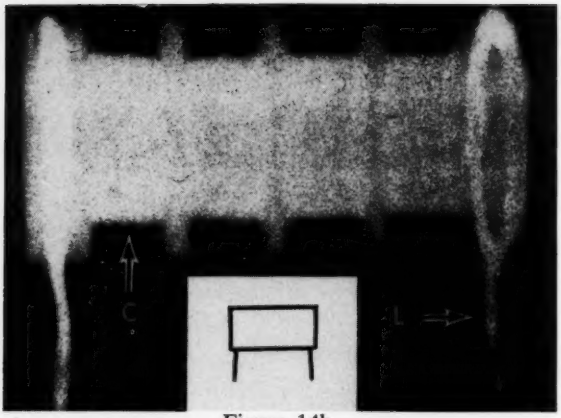

Figure 14b

Radiograph of a precision resistor made with the 3 mm silver phosphate compound source embedded in a lucite holder as shown in Figure 13. Subject's outline is shown.

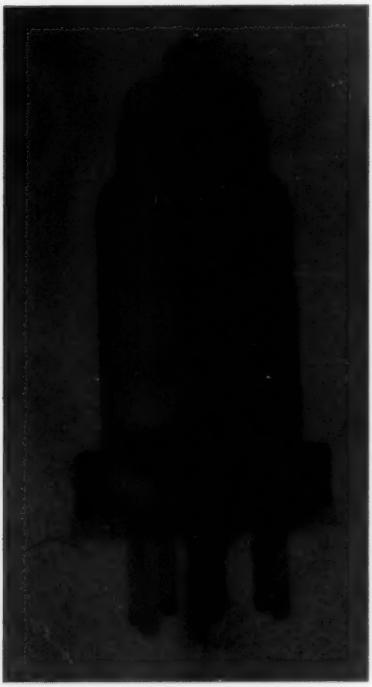

Figure 14c

Radiography of an all-metal tube with the compounded source-target.

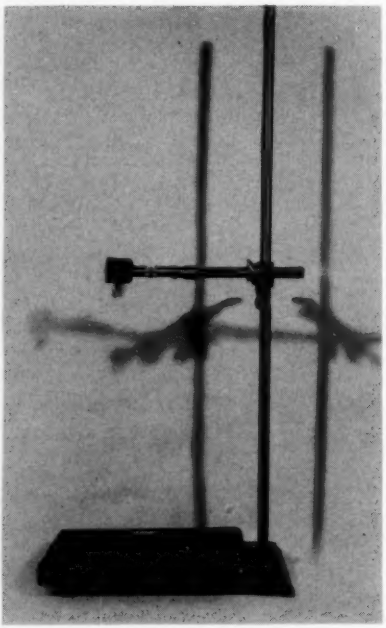

Figure 14d

An exposure in progress. This is the silver phosphate compound source.

visible are of 5 mil tungsten which indicates moderately good resolution (about 120 microns in diameter) for this unrefined laboratory set-up. The gradations in contrast and the continuous tone of the glass shield indicate that some X-radiation, of the low energy character desired, must have been produced. Some characteristics of this spectrum will be described in the following. Figure 14b is a similar exposure of a precision ceramic resistor which was made with a compounded silver phosphate source similar to the one described above. The metal end strips L are clearly visible. The inner core of resistance wire winding is delineated (arrow) as well as the segmented ceramic insulator disks. The paper cover is shown by the light line at the top and bottom. This is a positive copy of the radiogram. Some contrast may be observed between the various components of the subject. Because of its gross nature the inherent resolution is not well defined with this subject.

The exposures which are shown above were done with a low-level beta source and as a consequence the exposure times are relatively long. These times could be conveniently reduced by a factor of 10^2 by concentration of more P^{32} into the crystal lattice. This might reduce the exposure times to about twenty minutes. It might be possible to reduce this time still further (Brownell[14]).

A tendency towards 'flatness' or lack of proper contrast in these exposures may be attributed to the higher energy bremsstrahlung component of the total X-ray spectrum. This effect may be reduced by using a lower energy beta particle to reduce the $\frac{E\,Z}{800}$ ratio. Brownell[14] proposes that the homogenous source target is the best avenue for development of a radiography source with the desired contrast for resolution and differentiation of tissue and bone.

SUMMARY

The key to the usefulness of the X-ray photons from the beta-excited source lies in two characteristics; a, the intensity obtainable or rather the production efficiency; b, the spectral character of the total electromagnetic radiation obtained. Figure #15 is a copy of the spectral recording made from the compounded source described above. This tracing was done an a NaI recording, gamma ray, scintillation spectrometer*. The energy of the particulate radiation was high (in this case P^{32}). The target was of a relatively high Z number and thus the higher energies might be anticipated in the bremsstrahlung. These may be seen in the trace. No characteristic photons are evident in this spectra, which extends to about 400 Mev, but this may be masked by the inherent lack of resolution of the spectrometer. Further refinements are needed for both the planar copper target source and the compounded source to reduce the high energy component. Promethium-147 with tin targets has been proposed by Leboeuf and Stark, as a source favoring the lower energy, characteristic radiation of tin.

Table VIII gives some of the factors affecting the beta-excited source's efficiency and its photon spectra. The intensity of the X-radiation produced by the beta-excited source, or more accurately; the overall efficiency of the device, may be substantially improved by what we may term geometric factors. This includes better positioning be-

*Courtesy of the Phoenix Project, University of Michigan, Ann Arbor, Mich.

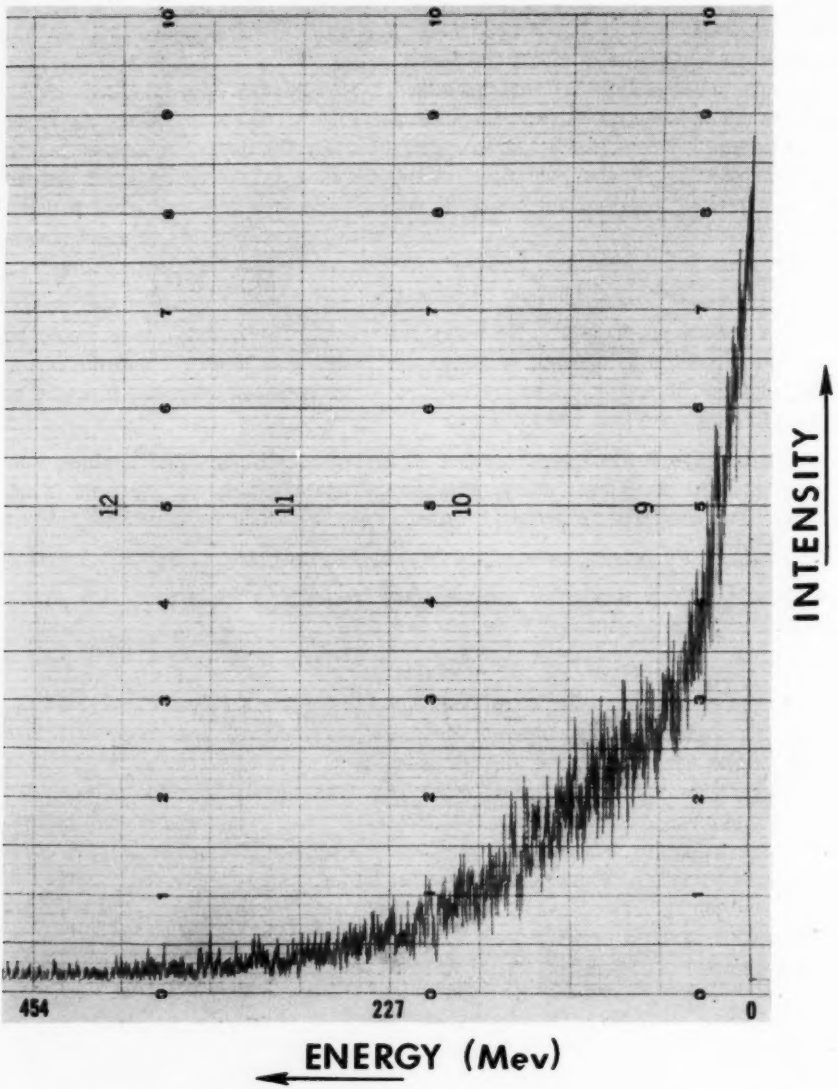

Figure 15

A scintillation spectrometer trace of the photon spectrum from the copper casing source shown in Figure 5. Energies range out to about 450 Kev. Energy is plotted right to left on the condensate; relative counts on the abscissa. This is a direct copy of the spectrometer trace which was run from right to left.

TABLE VIII

SOURCE IMPROVEMENTS

(1)	Spectral adjustments.
	a. Target Z.
	b. Beta-ray energy.
	c. Self absorption
(2)	Efficiency adjustments.
	a. Geometry (spatial).
	b. Target type.
	c. Source energy.
	d. Source configuration.
	e. Absorption and scatter characteristics.

tween the components of the source. The energy of the beta radiation and the target type are also concerned. In the case where bremsstrahlung, and particularly high energy bremsstrahlung, is to be minimized and characteristic X-ray production enhanced, the target Z should be kept as low as possible and the beta energy reduced by absorption techniques, shown earlier, or by careful selection of the proper natural beta energy. The problems of self-absorption and resonance absorption must be obviated by proper choice of the target material.

Some workers [14,13,7] have described beta excited sources applicable to diagnostic radiology. Other potential applications include; radiography, thickness gauging and analysis, density measurements, absorption chemical analysis, fluorescence analysis using the white spectra of the simple source. The source portability, small size, stability and zero power consumption indicate that the first real application of this source may be for radiography and radiology in the field or in other locations where power is not conveniently available. The low overall efficiencies which are currently available (10%[13] for the transmission target type and 1% for the reflection design) obviate this mechanism as a serious commercial competitor to the conventional X-ray device where electrical power is available, at least for the present time. The diagnostic X-ray tube operating at one millampere beam current may out-produce the one curie beta source by a factor of 10^4. The most recent report[14] on Pm^{147} compounded sources indicates that a factor of $2 \cdot 10^3$ exists between the diagnostic X-ray device and the promethium source type developed. Sacrificing some of the conventional performance expected of the radiological exposure, an improvement factor of about $6 \cdot 10^1$ is still essential. The portability, compact size and zero power consumption may eventually make this unit attractive for both analysis and radiology. An example in non-destructive analysis might be the study of the characteristics of suspension cable surfaces, where exposure time is not critical, on some inaccessible portion of a bridge. In such a location the small isotope-powered fluorescence target unit could be attached and left for many hours for exposure. An example in radiology could be emergency applications in disaster areas where power has been disrupted. In such a case some of ultimate in quality might be sacrificed. Here the beta-excited X-ray source could inform the physician of the gross condition of broken bones and immediate emergency care could be adjusted by this information.

The beta-excited X-ray source may also have some potential as a standardization unit for target characteristic radiation. It may be applied in teaching the principles of photon production and it has a distinct use in the experimental laboratory where a stable, inexpensive source of low intensity X-radiation is desired for varied research uses.

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Acknowledgements

This is to acknowledge the technical aid supplied by B. Buber, Physics Department and instrumentation loaned by A. Emmons and J. Coleman, Phoenix Project, University of Michigan; and fabrication by C. Bartrem and H. Wagner, Instrument shop, Henry Ford Hospital; and drawings by Art Department, Henry Ford Hospital.

COMMON VASCULAR PROBLEMS OF THE LOWER EXTREMITIES

PART I *Considerations in Vascular Insufficient States of the Lower Extremities: The Anatomic, Physiologic and Pathologic*

JOSEPH BENINSON, M.D.*

Modern day medical care has extended the life span of man and concomitantly, the incidence of degenerative disease. Not least in this progression is the ever increasing number of people who now live to acquire vascular insufficiency. Dr. Gunnar Bauer of the Marie Stadt General Hospital in Sweden, in discussing this problem at the Fourteenth Congress of the International Society of Surgery in Paris in 1951, estimated that one person in every five could expect to suffer from improper venous return from the lower extremities in one form or another and noted, "that with the exception of rheumatism, this condition (specially post-thrombophlebitic sequelae) heads all other illnesses causing invalidity."[1]

ANATOMICAL CONSIDERATIONS

Before embarking on the interaction between the structural, physiological and pathological forces involved in vascular stasis of the lower extremities, some fundamental knowledge must be reviewed. To do so, the author will draw freely on Burch's "A Primer of Venous Pressure."[2]

A review of the gross anatomy involved is afforded by Figures 1 and 2[3] which show the superficial and deep veins of the lower extremities and their relationship to the adjacent structures. It is evident that whereas the deep veins have the support of the muscle masses with their connective tissue envelopes and an outer connective tissue sleeve of considerable thickness, the superficial vessels, in the main, lie external to that outer sleeve having only the fat, subcutaneous tissue and skin for support.

The venous valves are almost without exception bicuspid in the lower extremities. These are spaced at intervals in both the deep and superficial veins as well as in the communicating veins. They are also to be found at the point where a vein emerges from a muscle just prior to the point at which it empties into a collecting vein; however, the intramuscular portion of this vein is avalvular. This mechanism constitutes the "peripheral heart" pumping station so that normally muscular contraction can spew blood under increased pressure into the venous circulation and speed the return to the heart.

Essentially, these valves are reflections of vein intima which develop early in fetal life in large numbers; however, many of these never reach full development and their number decreases as the fetus grows. After the infant is born the number of valves decreases with age so that when needed most they are present least. Actually, to date, no one has made an accurate study of the number of valves present in different age groups. Furthermore, Edwards and Edwards[4], and many other investigators have shown that following complete thrombosis of any vein of the lower extremities, there

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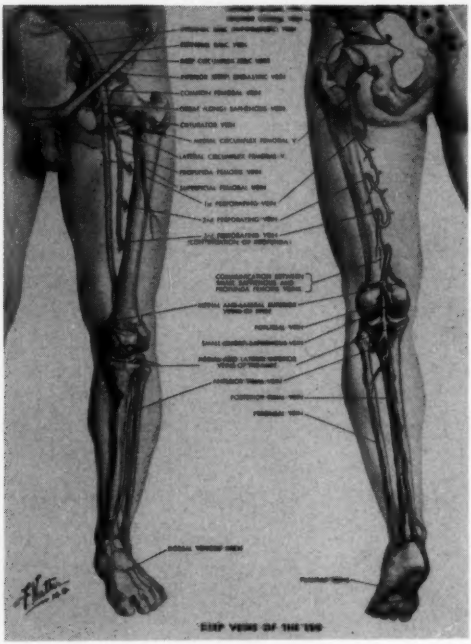

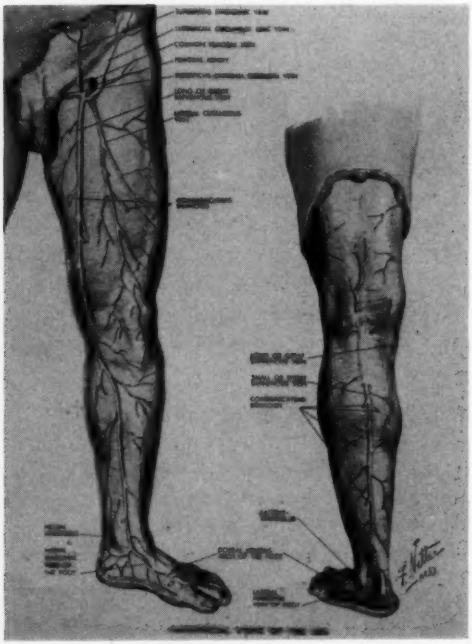

eventuates an anatomically and functionally valveless, rigid venous segment or entire vein with an irregular lumen. The valves of communicating veins or muscular veins are sometimes affected by this process simultaneously.

Histologically, the veins tend to be thin walled and wide lumined compared to the adjacent arteries. The thinner walls are the result of relatively small amounts of smooth muscle, elastic tissue and collagenous fibers being present, for veins consist largely of connective tissue. These three layers of intima, media and adventitia are preserved until the level of the venules and capillaries. It is perhaps significant that veins have a richer supply of vasa vasora than arteries, even down to those of 1.0 mm. diameter. Perhaps lowered oxygen tension and slowed flow dictate this richer supply and it would be of interest to know what part, if any, this blood supply plays in keeping the thrombosed vessels viable until they can recanalize.

Because of their thin walls, veins are pliable and tend to collapse almost completely when emptied of blood unless they are situated where connective tissue trabeculae act as guy-wires. These trabeculae tend to conteract the effect of rising tissue pressures proportionately. This is the case in the extremities.

The internal saphenous vein is wider distally than at is proximal terminus to allow for the inflow from the communicating veins which are most plentiful distally.[5] The communicating veins enter the deep veins at an oblique angle (toward the heart) and it is the incompetency of these communicating vein valves that Muir, Mucklow and Rains have demonstrated to be present in their study of varicosities by venography.

The lymphatics of the lower extremities are found in the dermis—in the superficial and deep plexuses particularly of the plantar skin of the foot—as well as along the superficial and deep vessels, in joint capsules, periosteum, bone and muscle tendons.[7] Their presence in muscles is disputed.

Most investigators believe that lymphatics begin as offshoots of blood vessels which soon lose their connections and then form capillary tubes which anastomose freely and have many cul-de-sacs. The capillaries themselves are avalvular but form collecting vessels which are richly supplied with bi- or tri-cuspid valves and these drain through regional lymph nodes and/or an occasional intercalated node. In both types of nodes the capillaries break up into wide-lumened capillary sinuses which again reform to produce collecting vessels on their way to the cisterna chyli, thoracic duct and the juncture of the left jugular and left subclavian veins.

Histologically, one finds the three layers as noted for the veins but lymphatic vessels are thinner, the layers less apparent, and in the normal lower extremities the collecting vessels are rarely more than 0.5-0.75 mm. in diameter. Anastomoses between collecting vessels are more frequent than they are in their companion veins.

It is believed that whereas the veins have marked regenerate powers, the lymphatics heal and regenerate slowly and that lymph nodes probably do not regenerate unless under pathologic stimulus.

A. J. Reyniers[8] and his group have clearly demonstrated the intriguing fact that the development of lymphoid tissue is definitely affected by the presence or absence of infection in the environment of the individual.

In man, it has been estimated that between 1½ and 3 liters of lymph flow through the thoracic duct in 24 hours. The majority of this comes from the liver and intestines. During rest the flow from the lower extremities is believed to be extremely small but it is increased by activity and massage. The rate of flow in pathologic states associated with vascular insufficiency of the lower extremities is not known.

Crissman and Blalock[9] report that pulsations transmitted from arteries to adjacent lymphatics also aid the return flow of lymph.

McMaster and Hudach[10] using vital blue dyes and following the streamers that develop in the lymphatics find that when the limb hangs down after injection, none or almost none of the dye streams heartward. If the subject be supine and at rest, then short, pale streamers develop slowly. Following massage, elevation of the leg or exercise they develop into rapidly moving, long, deep colored, lymphatic streamers. Following the release of venous obstruction with its reactive hyperemia, which latter is also seen following violent exercise, the largest, darkest and most rapidly moving streamers develop.

There are no streamers in patients with idiopathic lymphedema or in patients with cardiac decompensation. The latter apparently also have venous valvular decompensation probably caused by overdistention of the veins, for venous valves are said to become functionally patent if their diameters increase more than 40%. In cardiacs, the streamers can be made to go distally, by massage, which supports this possibility of valvular failure for this could not be accomplished in normal subjects. Similarly, with the onset of diuresis following nephrosis, marked streamer formation ensues. Further, McMaster and Hudach[10] show that every intradermal injection is in part a lymphatic injection and that the transport of foreign substances by lymphatics is more rapid than the volume of lymph flow indicates, for normally the lymphatics are flat and a little fluid moves a long way.

The exact role of the lymphatics in the lower extremities has not been detailed entirely; however, the work of McMaster,[10] Moyer and Butcher,[11] Kinmonth, Taylor and Harper[12] and others have clarified some of the thinking on this subject.

McMaster[13] points out that the formation of lymph takes place in the main through the walls of lymphatic capillaries and that the larger collecting channels act chiefly, if not entirely, as conveyors of this fluid to the blood. He as well as Field, Drinker and White[14] confirm the hypothesis of Gaskell and also of Starling that the intralymphatic capillary pressure is lower than the tissue pressure. This does not bring about collapse but rather expansion of the lymphatic capillaries for as tissue pressure mounts, the capillary walls — like most veins — have guy-wire-like fibrillar connections to the adjacent connective tissue elements and the vessel walls are pulled apart.

Lymph stasis as exemplified by phlegmasia alba dolens is caused by primary lymphatic obstruction. The veins have naught to do with the initial accumulation of lymphatic tissue fluid. Homans[15] and Homans and Zollinger[16] have demonstrated experimentally that ligation of the veins does not prevent the phlegmasic swelling from disappearing once the lymphatic obstruction is relieved.

PHYSIOLOGIC CONSIDERATIONS

Under physiologic conditions then, we have a closed system including the heart, arterio-venous vasculature and lymphatics which tend to follow the fluid principles as

set out by Poisseuille's and Bernoulli's laws. (For a simple explanation of these concepts see Burch's Primer[2]). Practically speaking, these laws explain why the venous pressure exerted is greater in smaller (peripheral) veins yet the force supported per unit length of these smaller veins is less than that on the veins close to the heart which have greater cross-sectional diameter (lateral pressure is proportional to surface area).

Eyster[17] gives a graphic representation of the hydrostatic pressures produced by standing, when he stranslates height into pressure, saying that for each vertical cm. in height the effect of gravity is equal to about 10 mm. of water or about 0.74 mm. of mercury.

This then makes for the physiologic, hydrostatic, pressure-gradient which is normally present in man.

The general factors affecting the normal return of blood from the tissues to the heart are:

1. Contraction of cardiac muscle
2. Pressure originating in the heart (vis a tergo)
3. Negative intrathoracic pressure
4. Relative volume of blood in arterial and venous systems
5. Venous tone
6. Gravity
7. Tissue pressure

The mean venous pressure in the lower extremity of a normal, erect, adult male varies from about 1400.0 mm. of water in the dorsalis pedis vein to about 1000.0 mm. of water in the upper end of the great saphenous vein.[2] Knowing about the phlebostatic level — that point (about the third interspace, at the sternum) where the venae cavae join and enter the right atrium under 0.0 mm. pressure — then makes it clear that whereas the normal, resting, supine individual has a mean venous pressure of 180.0 mm. of water at the ankle, the effect of standing is equivalent to adding thereto the hydrostatic pressure present in the length of a column of fluid from the dorsum of the foot to the phlebostatic level of the heart. In the physiologic state the weight of this column of fluid is distributed between the consecutive valves which divide the vein into pressure-segments[2].

A review of the literature reveals the following information regarding values under varying conditions in the normal veins of the lower extremities.

Pollack and Wood[18] report the direct, mean, venous pressures in the saphenous vein at the ankle (converted from mm. of mercury to mm. of water) in normal man to be as follows:

Recumbent position	158.0 mm. of water
Sitting position	756.0 mm. of water
Quiet, standing position	1172.0 mm. of water

This pressure shows an average drop of about 810. mm. of water with walking, and a return to normal in about 30 seconds after walking ceases. Thirty seconds is the time required for the blood capillaries to refill the veins when the valves are competent. This is the basis of the tests devised for venous incompetency.

This correlates reasonably well with Carrier and Rehberg's[19] report that the normal, average, direct, venous pressure (converted to mm. of water) in the dorsal vein of a relaxed foot hanging over the edge of a chair on which the patient is standing with the other foot is as follows:

0 time	860. mm. of water
5 minutes	970. mm. of water
6 minutes	1020. mm. of water
over 6 minutes	no change

During a 15 minute time interval the fluid loss into the tissues in this experiment distends the dependent foot from an initial circumference of 27.0 to 29.0 cm.

These volume figures correlate with the finding of Youman et al[20] that standing at a 75° angle for one hour causes the volume of the leg of normal subjects to increase over 25% without any pitting edema. This is accompanied by an increase of 18 — 40% in the serum protein concentration and an increase of 29 — 65% in the colloid osmotic pressure in the leg veins. From these figures they calculated that the increase in tissue pressure is three to five times as important in limiting fluid loss from the blood as is the increase in colloid osmotic pressure.

McMaster[21] found that in the slow edema associated with irritant chemicals or topical applications, the rise in the interstitial pressure of skin was slight. Also, he determined that the interstitial resistance of dermis in man could be measured directly by the edema fluid in the usual edematous skin and that it was about 5.0 mm. of water higher than interstitial pressure. In the boggy, edematous skin no measurement could be made, for although it appeared to feel like ordinary edema no free fluid was present.

Landis[22] listed the factors favoring edema formation and correlated them with clinical examples.

Montgomery and Zintel[23], in a recent compilation of the direct venous pressures just above the ankle in normal subjects with primary varices and in post-thrombophlebitics, noted that marked pressure differences were apparent only when the patient was walking.

In still another report, Wells et al[24] stated that the leg volume continued to increase over a 2½ hour period during quiet standing, with filtration continuing indefinitely in the skin and gastrocnemius muscles which they considered to be low pressure filtration areas, and that it ceased rapidly in the other muscles of the leg which they considered high pressure areas.

Henry and Gauer[25] studying the effect of temperature on direct venous pressure in the normal foot found that as the temperatures increased, the mean venous pressure rose until, when the subject was hot (35 - 40° C.), it greatly exceeded the pressure opposing filtration.

Indeed, Landis et al[26] listed the factors affecting fluid passage through capillary walls as (1) permeability of capillary wall (2) capillary pressure (3) colloid osmotic pressure of the blood (4) temperature and (5) tissue pressure.

The rate of filtration decreased as tissue pressure rose in sudden obstruction and

could in some instances be stopped entirely with resultant necrosis. With sustained venous obstruction McMaster[27] was able to demonstrate a rise of the interstitial pressure of the skin of the leg in man from a normal of 25. - 37. mm. water to 150. - 230. mm. water after 15-27 minutes. Some of his experimental subjects experienced a sensation of relief from congestion after about 20 minutes of sustained venous obstruction as if some tissue adjustment or some venous by-pass to the marrow had occurred preventing further rise in pressure.

PATHOLOGICAL CONSIDERATIONS

Any alteration of structure and/or function which impedes the normal return of blood and/or lymph from the peripheral circulation to the heart and specifically causes pathologic changes in the lower extremities would be pertinent to this discussion.

Foote et al[28] studying 200 unselected cases equally divided between the OPD and IPD at Massachusetts General Hospital to see what was the underlying cause of the bilateral edema of the lower extremities reported the following etiologies:

Out-Patient Cases	Nos.	In-Patient Cases	Nos.
Varicose veins	56	Congestive failure	60
(Varicose veins with obesity)	31	(Varicose veins with or without obesity or vice versa)	12
(Varicose veins without obesity)	25	Renal disease	7
Obesity alone	13	Nutritional	7
Cardiac failure alone	13	Hepatic cirrhosis	7
Lymphedema	4	Leukemia	2
Renal disease	3	Myxedema	2
Nutritional	3	Miscellaneous	3
Hepatic cirrhosis	2		
Miscellaneous	6		

Mahorner[29], in 1949, reviewing indurated leg and leg ulcers defined indurated leg as "any hardness or thickening of the skin and subcutaneous tissue resulting from edema" and listed the factors causing indurated leg as follows:

1. Post-thrombophlebitic edema
2. Varicose veins
3. Obesity
4. Trauma
5. Infection (pyogenic or fungous)
6. Lymphedema
7. Immersion leg
8. Arterio-venous communications
9. Systemic causes
10. Combination of the above

He noted that the most frequent cause was post-thrombophlebitic edema and he repeatedly emphasized the importance of preventing the recurrence of swelling in the leg day after day which he felt was the direct cause of indurated leg and its allied disorders. This symptom-complex: progressive edema, induration, ulceration and/or eczematization, when the end-result of thrombophlebitis, seems to be best summed up by considering these stages as all part of the post-thrombophlebitic syndrome.

Of even greater significance was his statement to the effect that, "It seems always fair and even important to tell the patient that whereas varicose veins can be improved by ligation, the tendency to develop varicose veins cannot thus be removed."

Hunter et al[30] studying 351 autopsies found thrombosis of the deep leg veins to be present in 52.7% of middle-aged to older patients who had to be in bed for

varying periods of time. The majority of the thromboses were in the larger veins and were more frequent in the soleus than the gastrocnemius with a slightly greater tendency to occur in the right leg. Thromboses were more frequently bilateral than unilateral in their series.

Gunnar Baur,[1] the moderator of his section on post-thrombophlebitic sequelae at the 1951 International Congress of Surgery quoted the following:

1. A review of 100 cases of phlegmasia alba dolens in 1942 at the Marie Stadt Hospital showed that after 10 to 15 years all of the patients had edema in the leg, that 9/10's of them had indurated skin changes and 4/5's had ulceration.
2. Zilliacus in 1948 reported pronounced and often severely disabling sequelae in 90% of 680 follow-up cases. In 510 of these patients he found that at least 81 had to change their occupation and 54 had become definitely unfit for all kinds of work.
3. Sturup reporting from Denmark in 1950 noted in his post-thrombophlebitics, there was a recurrence rate of ulceration at least once every second year, hospitalization every fourth year and that these people were unable to work for about 25 days out of each year.
4. Birger in the 1941 report based on figures from the Swedish Pensions Board noted that as a cause of incapacity, this affection came a bit ahead of such important disease groups as tuberculosis of joints or bones and diabetes mellitus.

In recent reports Moyer and Butcher[11] and Butcher and Hoover[31] extended McMaster's work to demonstrate the following features about the superficial cutaneous lymphatics in addition to their being obliterated by sterile inflammation and showing regrowth following incisions.

The lymphatics were usually absent in skin about stasis ulcers and over "hard lymphedema" but were dilated over soft lymphedema. They were normal over simple varicosities and in cardiac and nutritional edemas. In split-thickness autografts they were at first dilated and if the graft was to survive, the lymphatics had to survive and establish connections with adjacent skin lymphatics. Following simple incision and closure, these lymphatics would by the 12-14th day post-operatively establish these connections if healing was by primary intention. In healing by secondary intention the lymphatics were fewer in number and smaller in caliber because of the scar.

The absence of superficial cutaneous lymphatics was associated with hyperkeratoses, collagenous and fibrous hyperplasia of the dermis, fibrous dysplasia of the subcutaneous fat and collagenous hyperplasia of the enveloping muscular fascia.

Despite all these findings there is a paucity of literature on values for the normal and abnormal lymphatic pressures in the lower extremities and the role of the deeper lymphatics in these problems other than in phlegmasia alba dolens.

For the various vein anomalies of the lower extremities and a discussion of the hereditary factors leading to venous difficulties the author refers the reader to any standard text on the subject.

SUMMARY

The basic anatomical, physiological, and pathological considerations have been reviewed and their inter-relationship stressed. The relative inadequacies of our present-day information in some of these fundamental facets have been either pointed out or inferred in the hope that other investigators might see fit to fill these gaps.

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THE NEUTRALIZATION OF GASTRIC ACID BY BILE TRANSPORTED THROUGH JEJUNAL TRANSPLANTS
PRELIMINARY REPORT

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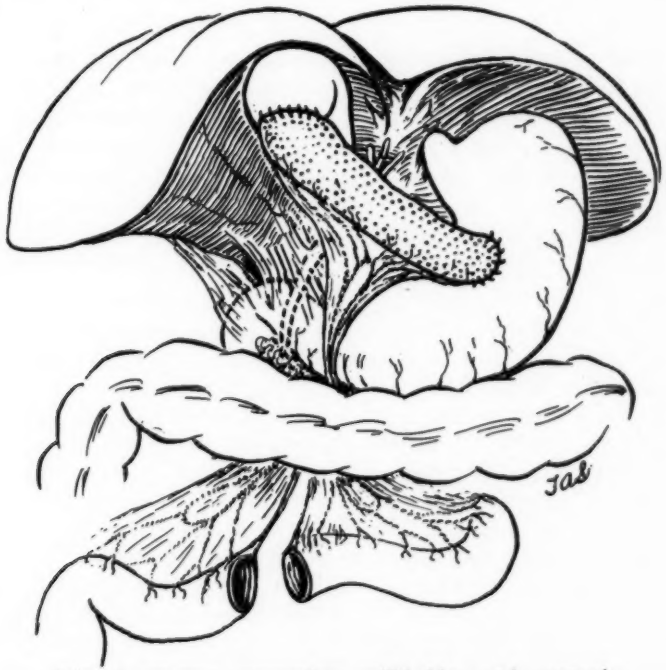
EDWARD J. GRAY, M.D.* AND FRANK H. DUFFY**

Duodenal ulceration presents a very common problem. The widely divergent views in regard to treatment speak for themselves more eloquently than any language of the lack of any completely adequate method of treatment. All methods of treatment have as their common goal the neutralization of gastric acid. Few would argue with the statement that there is considerable room for improvement in both medical and surgical methods of treatment for the all too common problem of duodenal ulceration.

The idea of using bile to neutralize gastric acid is not new. In the past, the usual procedure has been to anastomose the gallbladder to the stomach. This has been done under tension and in the majority of cases, stenosis of the anastomosis has taken place. Many extensive investigations have shown the ability of bile to neutralize gastric acid.



Jejunal segment connecting gallbladder and stomach. The segment keeps the original blood and nerve supply.

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In this preliminary report, we would like to present a method which we have been using on dogs in the Surgical Research Laboratories at the Henry Ford Hospital. This method has utilized a transplant of jejunum with its own blood supply connecting the gallbladder to the stomach. The normal pH of bile in dogs has been found to vary from 5.8 to 8. The average pH in the dog's stomach has been found to average pH of 1 to 1.5. Human bile tends to be more alkaline than dog bile and should produce equal or better neutralization.

The jejunal transplant has enabled us to avoid any tension on the anastomotic lines with no tendency toward stenosis. No disturbance in the anatomical locations of the organs involved has been noted. Bile is present at all times in the jejunal transplant and stomach. By using these jejunal transplants in an isoperistaltic manner, we have been able to produce rather striking reductions in the free Hc1 concentration in the stomach. In the majority of dogs we have changed the gastric pH from 1 to 1.5 up to 4.5 to 5.5 This obviously represents quite a reduction in gastric acidity.

Experimental studies are still under way. Only time will give the final answer as to the practical application of this method in the all too common problem of duodenal ulceration.

OTOTOXICITY IN CATS FOLLOWING TOXIC DOSES OF STREPTOMYCIN

T. MANFORD MCGEE, M.D.*

The toxic effects of streptomycin sulfate in patients on long-term therapy have been observed by many clinical investigators. The toxic effect usually is centered around a dysfunction of the vestibular mechanism, and is manifested by ataxia and vertigo[1,2,3,4]. Many patients receiving large doses have experienced temporary hearing loss and a few have sustained permanent partial deafness[1]. A number of investigators have subjected animals to toxic doses of streptomycin, but their observations conflict as to the site of the organic lesion. Causse,[5] Hawkins[6] and Berg[7] have described degenerative changes in the vestibular sense organ and organ of Corti. Christensen et al,[8] and Winston et al,[9] on the other hand, concluded that the organic changes were in the vestibular neural pathways.

A controlled study was designed to further clarify the site of the toxic effects of streptomycin and relate the lesions to alterations in vestibular and auditory functions. Pathological studies of the inner ears have been completed in some of these animals, and the organic changes in the sense organs can be correlated with the functional alterations.

The experimental group consisted of 7 healthy adult cats. Each cat had one ear surgically destroyed. Following recovery from this procedure, base-line vestibular tests and audiograms were made. In the test of vestibular function the animals were placed on a rotating table with the head over the axis of rotation of the table, turned at the rate of 1 turn per second for 10 seconds, and abruptly stopped. The duration of post-rotational nystagmus was determined for turning to both right and left. This test, carried out in the horizontal plane of the head, indicates the functional state of the crista of the horizontal canal.

Base-line cochlear function was evaluated by obtaining a series of reproducible audiograms for each animal before, during and following treatment with streptomycin. These were done utilizing conditioned response techniques[10] by which the animals are trained to avoid shock by moving forward in a rotary cage in response to auditory stimuli. Because the objective of the experiment was to study toxic effects, the dosage and duration of administration varied considerably in the different animals, with the functional tests serving as a monitoring method for determining the state of toxicity. The animals were injected intramuscularly with strephomycin sulfate (Squibb) in doses varying for the different animals from 25 mg. per kilogram to 200 mg. per kilogram per day in two equally divided doses. When the desired toxic effects had been obtained the animals were kept for one year, sacrificed by intra-vital perfusion, and the ears and brains prepared for pathological study.

Results: Four of the 7 animals experienced a permanent high tone hearing loss at the completion of treatment. Six cats exhibited a loss of post-rotary nystagmus, but in 3 of these there was partial return (Table I). Ataxia developed simultaneously with the loss of post-rotary nystagmus. The animals tended to fall to one side, and walked

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Table 1

Cat no.	Dosage mgm/kgm	Days given	Total Dose Gms.	Post-rotary Nystagmus Day lost	Recovery	Hearing*
1	25	84	5.04	0		Loss perm.
2	50	36	5.04	95	partial 210 da.	normal
3	75	29	8.12	30	partial 82 da.	loss temp.
4	100	18	7.2	28	partial 125 da.	loss perm.
5	200	9½	7.78	12	no	normal
6	200	11½	9.66	11	no	loss perm.
7	200	28	19	11	no	loss perm.

*All hearing losses were limited to high frequencies.

with a wide base, or refused to walk at all. They could not be persuaded to jump and had peculiar searching movements of the head. The ataxia was severe for 2-3 weeks, after which there was gradual improvement, but even at the end of one year the gait had not returned to normal. All animals demonstrated a weight loss while receiving the drug.

The findings in two representative animals will be presented:

Cat 3 received 75 mg. per kilogram of the drug for 29 days. Post-rotary nystagmus for turning both to the right and left was lost on the 30th day. Partial recovery on turning to the right was noted on the 82nd day after the drug was stopped (Fig. I.). There was a temporary high frequency deafness, but the auditory thresholds were normal after several weeks (Fig. II.). The cat was killed one year after drug administration and the cochlea was found to be normal (Fig. III.). There was near-total loss of hair cells of the cristae of all three semi-circular canels and the utricle and saccule. These pathological findings were consistent with the ataxia and loss of post-rotary nystagmus.

Cat 7 received 200 mg. per kilogram per day of streptomycin and lost post-rotary nystagmus on the 11th day of treatment (Fig. IV.). The drug was administered for 28 days. A high tone hearing loss appeared on the 20th day and remained during the 1 year observation period (Fig. V.). Ataxia was severe, and remained so until the animal was sacrified. Histological examination revealed almost total loss of hair cells in the basal 7 mm of the cochlea and partial loss in the 12-17 mm region (Figs. VI & VII.). The sensory epithelium of the cristae and maculae was severly degenerated throughout with no hair cells remaining. (Fig. VIII.).

Summary: Toxic doses of streptomycin sulfate damage first the sensory epithelium of the vestibular labyrinth (i.e. cristae and maculae) and if administration of the drug is continued the organ of Corti is also affected. The first order neurones of the vestibular and cochlear systems do not appear to be affected directly by the drug.

Studies of the higher pathways in the brain have not yet been completed. The persistent severe ataxia manifested by some of the animals leads us to wonder if

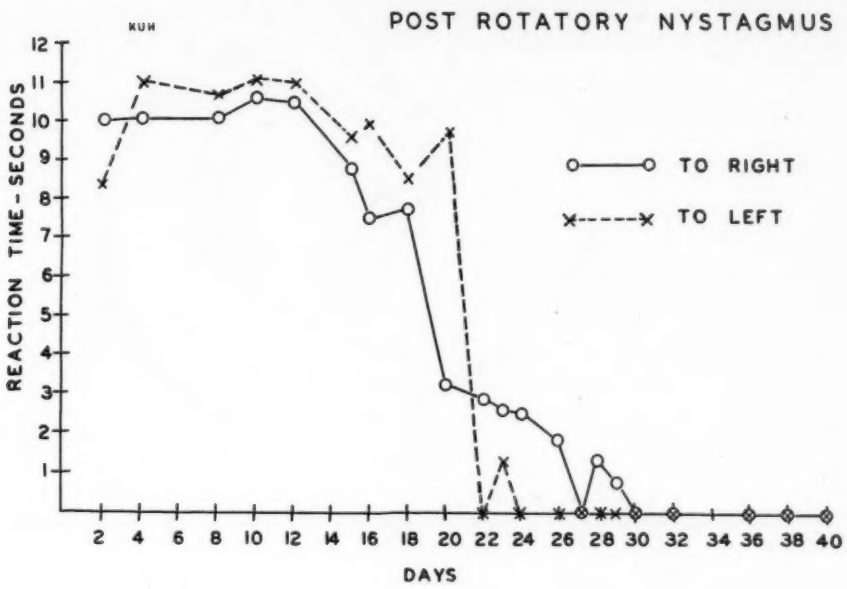

Figure 1

Cat 3. Post-rotary nystagmus in seconds is plotted as a function of time in days after the onset of streptomycin treatment. Dosage: 75 mgm per kilogram per day for 29 days.

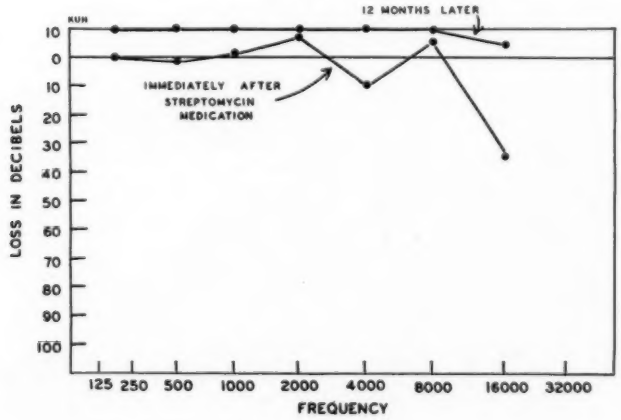

Figure 2

Cat 3. Audiograms taken immediately after streptomycin treatment revealed a high tone loss. After 3 weeks the hearing had returned to normal and remained so.

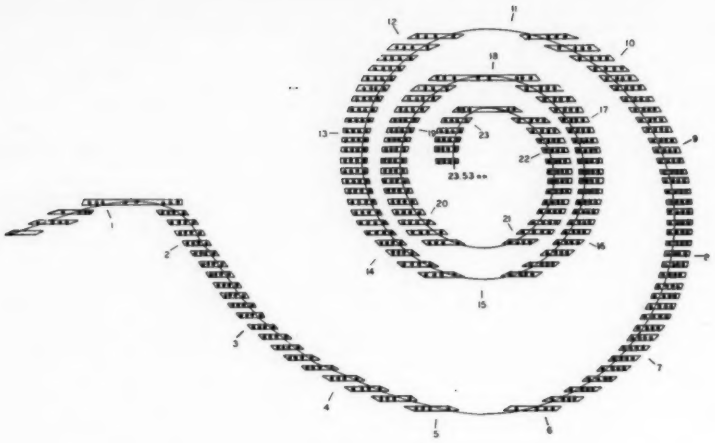

Figure 3

Cat 3. Graphic reconstruction of the cochlea, showing normal numbers of hair cells (black dots) throughout.

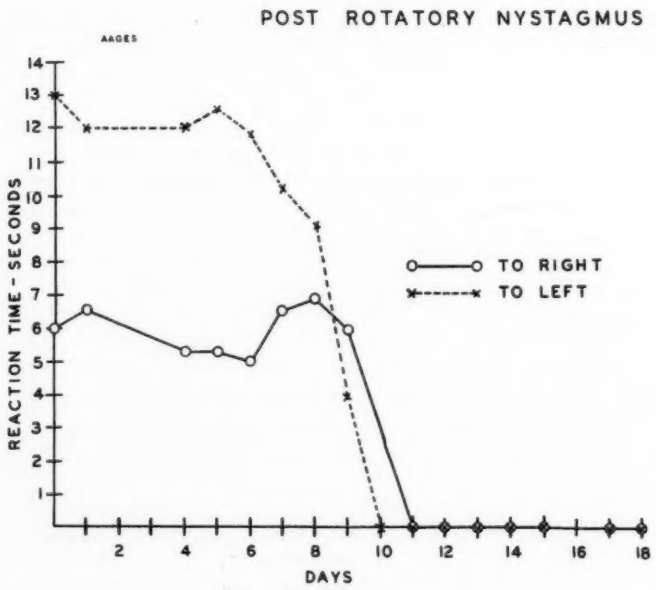

Figure 4

Cat 7. Received 200 mgm per kilogram per day for 28 days. There was no recovery of post-rotary nystagmus during the one year observation period.

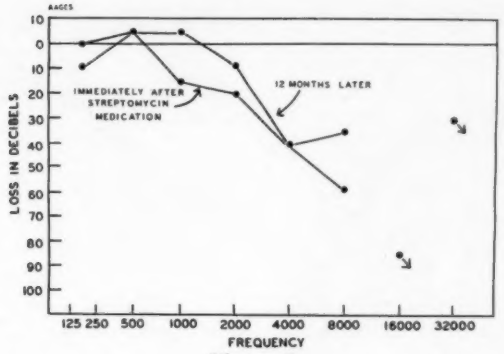

Figure 5

Cat 7. A high tone hearing loss persisted for 1 year after streptomycin treatment.

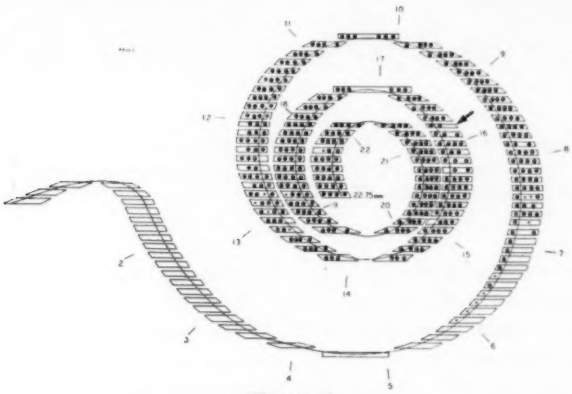

Figure 6

Cat 7. Graphic reconstruction showing complete absence of hair cells in the lower basal turn and a partial loss in the 12-17 mm region.

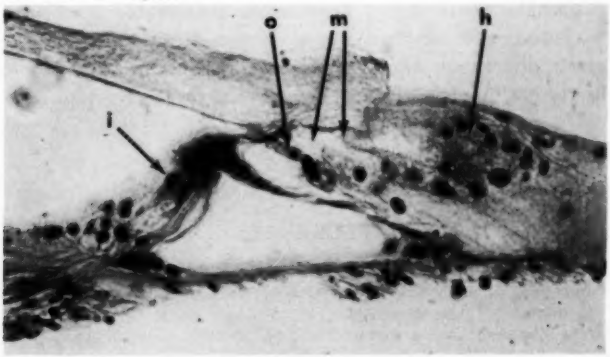

Figure 7

Cat 7. Organ of Corti, from the 16 mm region (see arrow, Fig. 7) "I" indicates normal inner hair cells, "O" the normal first outer hair cell, "M" the location of missing outer hair cells, and "H" the flattened Hensen's cells with granular cytoplasm.

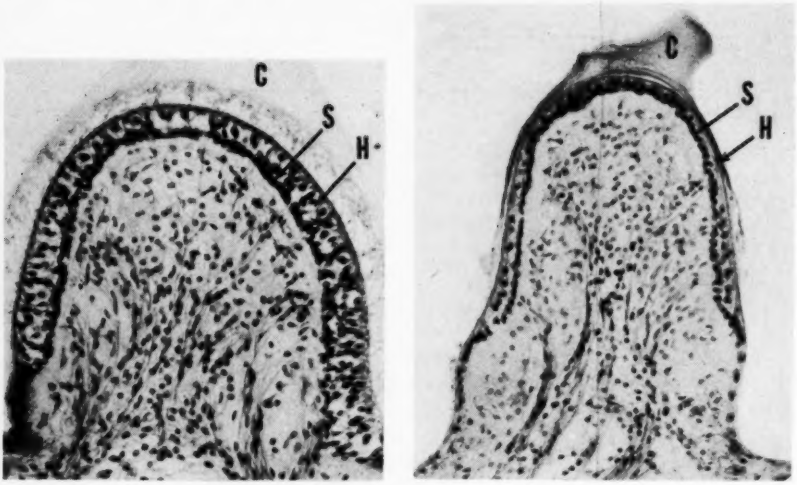

Figure 8

On the left the crista of the horizontal semi-circular canal of a normal cat. On the right is the crista of the horizontal semi-circular canal of Cat 7 showing degeneration of hair cells. "C" indicates the cupula, "S" the row of supporting cells, "H" the hair cells.

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there may not be some brain changes. On the other hand, it may be that cats compensate for vestibular losses less well than humans because of the relatively greater importance, for them, of the vestibulo-spinal pathways; i. e., the neck reflexes are better developed in the cat. This may account for the fact that cats have a permanent head tilt after destruction of the labyrinth, and peculiar, rolling, searching movements of the head following destruction of the labyrinth with streptomycin (not true of humans). The experiment has shown that streptomycin sulfate has a direct toxic effect on the vestibular and cochlear sense organ. Because the measurable functional deficits are consistent in magnitude with the degenerative changes in the sense organ, it is doubtful that there is also a direct toxic effect on the brain. Studies are now in progress to determine whether or not the drug also has some effects on the central nervous system.

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BACTERIAL SUSCEPTIBILITY TO ANTIBIOTICS

JOSEPH P. TRUANT*

The determination of *in vitro* susceptibility testing of bacteria to antibiotics has been of considerable value in assisting the clinician to choose the most effective therapeutic agent in order to overcome an infectious process. A great deal of valuable time may be lost, often to the detriment of the patient if bacterial cultures and *in vitro* susceptibility tests are not initiated as soon as possible. The information gained by following this procedure is not only important as an aid in determining which antibiotic may be effective against a possible pathogen, but also which antibiotics are ineffective.

As the scope of antibiotic therapy has been expanded by the discovery and development of many new chemotherapeutic agents, the problem of selecting the most suitable one for any individual case has become more and more complex. As a result, the following system has been adopted in the bacteriology laboratory. Routinely, with requests for sensitivity, the pathogenic bacteria are tested in one, two or possibly three stages. If stage one shows the organism to be sensitive to one of the antibiotics tried, stage two will not be undertaken unless there is a specific request by the clinician.

For Gram-positive bacteria, the first stage includes testing with sensitivity discs which contain penicillin, dihydrostreptomycin, tetracycline and chloramphenicol. In the second stage erythromycin, novobiocin and occasionally oleandomycin (matromycin) are employed. In reserve are such anti-bacterial agents as bacitracin, furacin, furadantin, neomycin and the sulfas which are employed only after consultation with the clinician.

For the Gram-negative bacteria the first stage includes dihydrostreptomycin, tetracycline and chloramphenicol. Strains of *Proteus* are tested with penicillin and *Pseudomonas* strains are tested with polymyxin in addition to the mentioned antibiotics during the first trial. In the second stage the clinician may choose from the following: furacin, furadantin, neomycin, polymyxin and the sulfas.

The sensitivity of any given strain or organism to an antimicrobial agent is generally defined in terms of concentration of the agent which inhibits the growth partially or completely. Several methods of determining this value are in common use and the results obtained by the different methods may show some discrepancy, depending on the details of the method and the choice of end point.

In this laboratory, we employ the disc technique since it provides a satisfactory and practical routine procedure for the sensitivity evaluation of microorganisms to a variety of chemotherapeutic agents. The antibiotic discs most commonly employed are listed in Table I. It should be emphasized that this technique is a qualitative procedure and is designed to determine whether the organisms are sensitive or resistant according to the following scheme:

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Sensitive — a marked zone of inhibition around the discs of both high and low series.

Moderately sensitive — minimal if any detectable zone of inhibition around the low series disc and a distinct zone of inhibition around the high series disc.

Resistant — absence of a zone of inhibition around the discs of both concentrations.

TABLE I

CONCENTRATIONS OF ANTIBIOTIC DISCS

	Low series	High Series
Penicillin	2 units	10 units
Dihydrostreptomycin	10 mcg.	50 mcg.
Tetracycline	5 mcg.	30 mcg.
Chloramphenicol	5 mcg.	30 mcg.
Erythromycin	2 mcg.	15 mcg.
Novobiocin	5 mcg.	30 mcg.
Oleandomycin	2 mcg.	15 mcg.
Neomycin	5 mcg.	30 mcg.
Polymyxin	5 mcg.	30 mcg.
Furacin	100 mcg.	100 mcg.
Furadantin	100 mcg.	100 mcg.

During the past year our interest has been centered on methods for controlling the variables inherent in routine disc sensitivity testing. A large number of Gram-positive and Gram-negative isolates from the routine services were tested for sensitivity to several antibiotics by three different methods. In this manner it was possible to reveal the frequency, extent and direction of the variations in the results obtained with the different procedures as applied to antibiotics which are now in general use. It was hoped, in this manner also to elucidate some of the factors responsible for the discrepancies which occur occasionally.

MATERIALS AND METHODS

Two hundred and thirty bacterial strains and ten antibacterial agents were included in this study. The three methods which were employed for susceptibility testing were as follows:

(1) The filter paper "disc agar diffusion" technique
(2) The tube or broth dilution technique
(3) The cylinder-plate method

The details concerning these procedures are clearly discussed by Grove and Randall (1) as well as by Jackson *et al* (2).

In order to obtain the best comparison and evaluation of the different methods, the tube dilution and the cylinder-plate tests done with any given combination of organisms and antibiotics, were set up and carried out using the same seed culture and the same freshly prepared dilutions of antibiotics. From three to six organisms were tested with the antibiotics at one time. The tests employing the medicated discs were carried out separately in our laboratory and some strains were also tested by the Division of Laboratories, Michigan Department of Health. The results were also compared with those reported by the technicians on the routine services.

RESULTS

It is not feasible to record the results of all tests with every combination of organisms and antibiotics included in this study. However, sufficient data will be reported in tabular form to illustrate the highlights which were brought out by this investigation.

Table II shows the results of testing 130 staphylococci against penicillin, tetracycline, dihydrostreptomycin, chloramphenicol, oleandomycin, erythromycin and novobiocin by the three methods. Inspection of the data shows only small differences in the values obtained by the different procedures. Thus, in almost all instances, agreement was observed. Minor discrepancies (one-dilution differences) occasionally would have altered the reporting in lieu of changing the sensitivity pattern from one category to another. This is practically only important with organisms on the borderline between moderately resistant and resistant, since the latter interpretation would exclude therapy.

The antibiotic spectrum of the staphylococci shown in Table II may be of practical value since it is based on a large number of recent isolates obtained from specimens collected in this hospital. From this spectrum it can be seen that as many as 78.8 per cent of the isolates may be resistant to penicillin. The spectrums of the other antibiotics shown in Table II correspond to those reported by other investigators.

Table III shows the results of the susceptibility tests with the Gram-negative bacilli. The data shows a greater variation in the sensitivity pattern due to the different methods than the results obtained using similar procedures against the staphylococci. The greatest discrepancy occurred with dihydrostreptomycin using the tube dilution procedure. According to Garrod (4) and others, the levels of resistance to streptomycin with *in vitro* susceptibility tests may vary with changes in the size of the inoculum. Branch et al (5) have shown that the size of the inoculum is an important factor in changing the minimum inhibitory concentration in the tube dilution method and it also has a slight effect in the agar well method but has not been found to exert any demonstrable changes in the reading of the 'disc results'. Furthermore, as already noted by others (2, 3), additional factors such as media, period of incubation, choice of size of inhibition zone etc. may account for some of the variation in the results shown in Table III.

The data in Table III shows dihydrostreptomycin and furacin were the most effective antibiotics *in vitro* against the Gram-negative bacilli. The least effective of the five agents was tetracycline. Previous experience has shown that penicillin is ineffective against this group of organisms. Occasionally high concentrations of penicillin will inhibit members of the genus *Proteus*.

TABLE II

COMPARATIVE TESTS BY THREE METHODS ON 130 STAPHYLOCOCCI

METHODS	Penicillin	Tetracycline	Dihydro-streptomycin	Chloramphenicol	Natromycin	Erythromycin	Novobiocin
DISC							
% sensitive*	21.2	42.4	44.3	90.0	97.7	93.4	100
% resistant**	78.8	57.6	55.7	10.0	2.3	6.6	0
TUBE DILUTION							
% sensitive	18.2	42.4	44.3	88.6	97.7	90.4	100
% resistant	81.8	57.6	55.7	11.4	2.3	9.6	0
CYLINDER-PLATE							
% sensitive	22.7	39.4	44.3	87.1	95.5	93.4	100
% resistant	77.3	60.6	55.7	12.9	4.5	6.6	0

* Organisms inhibited by the range of concentrations listed in Table I for each antibiotic.

** Those species which are not inhibited by the antibiotic concentration shown in Table I.

TABLE III

COMPARATIVE TESTS BY THREE METHODS ON 100 GRAM-NEGATIVE BACILLI

	Tetracycline	Dihydro-streptomycin	Chloramphenicol	Furacin	Furadantin
METHODS					
DISC					
% sensitive*	36.2	80.0	67.5	82.0	54.5
% resistant**	63.8	20.0	32.5	18.0	45.5
TUBE DILUTION					
% sensitive	42.5	62.3	60.0	75.0	50.0
% resistant	57.5	37.7	40.0	25.0	50.0
CYLINDER-PLATE					
% sensitive	37.5	73.8	60.0	73.0	63.6
% resistant	62.5	26.2	40.0	27.0	36.4

* Organisms inhibited by the range of concentrations listed in Table I for each antibiotic.

** Those species which are not inhibited by the antibiotic concentrations shown in Table I.

DISCUSSION

Certain conclusions are apparent after an examination of the foregoing data. As might be expected, discrepancies do occur among *in vitro* results which have been obtained by different methods. None of the procedures lend themselves to accurate quantitation, although reliability and accuracy can be increased by multiple replications, this approach is generally impractical for the routine bacteriological laboratory.

It is not meant to imply that tests for susceptibility of bacteria to antibiotics have no value whatever. It is more proper to infer from our experiences and those of other investigators that the tests can be used as a general qualitative guide to distinguish susceptible from non-susceptible organisms.

The disc was designed for simplicity and not for a high degree of accuracy. It appears to be adequate for all practical purposes since numerous reports attest to the fact that the results obtained by the disc mehod correlate well with clinical experience.

The tube dilution method gives an end point reading and demonstrates the minimum inhibitory concentration (M. I. C.) of the antibiotic. While the information is reliable within the limits of error inherent in such a procedure, the method has serious drawbacks. These include the large amount of equipment, material, time and effort consumed in testing the sensitivity of an organism to several antibiotics. Therefore, the tube dilution procedure is employed only in situations wherein 'quantitative results' or synergistic studies with two or more drugs are of considerable clinical importance.

The cylinder-plate assays compared favorably with the results of the other two methods. This technique has the disadvantage of being more laborious than the disc method but, like the tube dilution procedure, it has the advantage of being more reliable and accurate. However, the cylinder-plate method is not as yet a practical procedure for routine susceptibility testing although it is extremely useful as an experimental tool.

Susceptibility studies which have been performed over a period of years with such groups of organisms as Meningococcus, Gonococcus, Pneumococcus, Hemophilus and Streptococcus pyogenes (Lancefield Group A) have been more or less uniform in their sensitivity to many antibiotics. The situation is entirely different with a number of other organisms such as the staphylococci, enterococci, coliforms, *Proteus, Pseudomonas* etc. which vary widely in this respect. For this reason, standard sensitivity tables reported in the literature or distributed by pharmaceutical houses cannot be relied on for the selection of antibiotics most apt to be successful in treating this group of bacteria.

SUMMARY

The susceptibility patterns of two hundred and thirty organisms to ten antibiotics have been examined by means of three methods. The data shows some degree of variation due to the different testing techniques. The value and limitations of the results of susceptibility tests to antibiotics are discussed, particularly with respect to their clinical application.

ACKNOWLEDGMENT

I wish to express my appreciation to Alex Dombroski and Alex Mercer for technical services.

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PROTEIN ELECTROPHORESIS

E. F. WILT, M.D.* AND N. C. BRADY, M.D.*

Some background and clinical applications of serum electrophoresis are presented with particular emphasis upon technic of filter paper electrophoresis as performed in the laboratory of Henry Ford Hospital. The ability to separate the components of a protein mixture by means of electrophoresis is based upon the fact that on the individual protein molecule, in either an acid or alkaline solution, is carried an electrical charge. Therefore, it is possible to cause the migration of these molecules in an electrical field to either the positive or negative pole. The rate at which migration occurs is to a large extent determined by the size of the individual molecular charge. Furthermore, it is known that the size of the individual electrical charge on the protein molecule varies from one protein species to another. This basic principle underlying all of clinical electrophoresis was well known as early as the beginning of the 19th century. At that time physicists and chemists noted that it was possible to cause the migration of a colloidal solution through a clay filter in the presence of an electrical current. During the early years of the present century numerous investigations utilizing the technic were carried out on microscopic size particles such as red blood cells and bacteria as well as the separation of the components of *colored* colloidal solutions. However, the problem of separating sub microscopic sized particles such as protein molecules as well as the separation of the components of *colorless* colloidal solutions remained.

As a solution to the problem Aerne Tiselius in 1937 introduced a method which made use of a complicated optical system and took advantage of the differential refractive indices of the separated proteins. He was able to photograph the individual bands of optical density caused by the protein segments as they migrated through solution. This technic proved to be an extremely effective one, allowing for the rather exact separation of individual proteins in solution. Unfortunately, it was limited in its clinical application because of the time consumed in individual analyses and the expense of the apparatus involved.

A method for measuring serum albumin and globulin known as the "salt fractionation" method had been used by clinicians for many years. With this technic the globulin fraction of the serum is chemically precipitated from solution and measured separtely from the albumin which remains in solution. The technic is simple but subject to some definite errors. For instance, a portion of the globulin fraction frequently fails to precipitate from solution, particularly the alpha 1 globulin fraction which remains in solution with the albumin. The globulin fraction is determined along with the albumin, giving rise to falsely elevated levels of serum albumin and conversely low values for serum globulin.

The method of determining the distribution of serum protein by means of filter paper electrophoresis which was developed about 1950 represents a compromise between the relatively precise but tedious and expensive method of Tiselius and the more simple but inaccurate "salt fractionation" method. Because of its simplicity and accuracy, filter electrophoresis has had wide clinical use.

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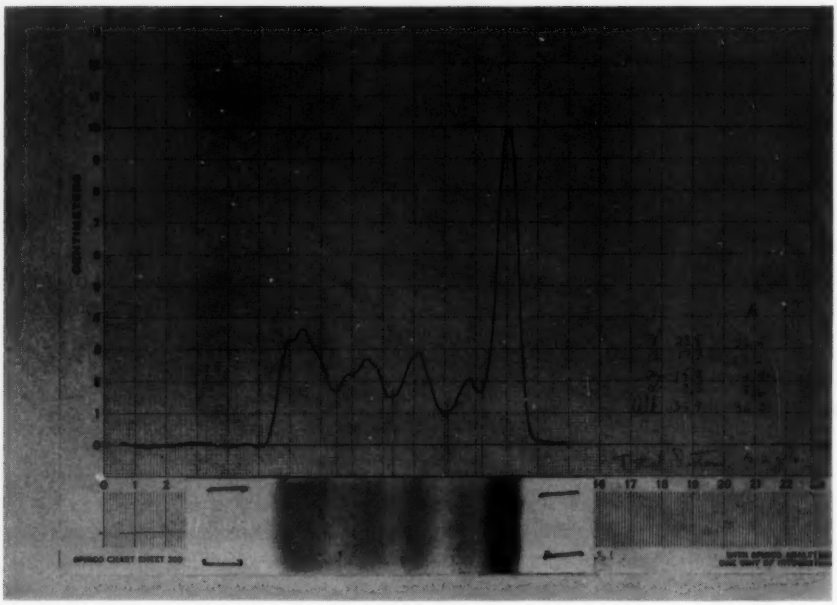

Figure I

Normal pattern with report.

Figure I is a representation of a fairly normal distribution of adult serum proteins. You will note the strip of filter paper at the bottom with the dark staining bands of separated protein material, while above we have the graphic representation of these segments of protein. On the far right, representing the most rapidly migrating serum protein is the serum albumin, normally representing between 45 to 62 per cent of the total protein. Next is the alpha 1 globulin, normally between 3 and 7 per cent of the total. Next, the alpha 2, approximately 6 to 13 per cent. Then the beta globulin, between 9 to 18 per cent. And finally, the slow moving gamma globulin, ranging between 11 and 22 per cent.

In actual practice the strip of filter paper is impregnated with an alkaline buffered solution and a carefully measured amount of serum protein is applied to the paper. The filter paper is again immersed in the alkaline solution and an electrical current is passed through the solution. The protein is allowed to migrate across the filter paper over a period of 16 hours, at the end of which time a bromphenol dye is applied to the filter paper. This dye is bound fast to the free amino groups of the protein molecule, thereby affording a visual representation of the separated protein increments. The filter paper is then dried and subjected to a photoelectric cell analysis which measures the optical density of the various portions of the paper and constructs the linear graph which you see in Figure I. Finally the various segments of the graphic curve are separated by the pencilled lines which you see, the area beneath the curve is computed and the values reported as percentage of total protein. The total protein

itself is determined by a colorimetric method entirely separate from the electrophoretic analysis. As you can see, the filter paper technique itself is subject to some error. In some cases it may be quite difficult to decide at what point the lines separating each segment of the graph should be made and the selection is often quite arbitrary. Also it can be noted that there is some blue staining protein material on the filter paper lying between the more definite bands of protein, and it is well known that a certain portion of the protein is absorbed on the filter paper during its migration. This is particularly true of the serum albumin. This source of error is to some extent being obviated by the introduction of a thinner filter paper, to which less of the protein material is absorbed.

Some of the generalizations which have been made in the literature regarding this subject follow. In a large series of cases reported in 1956 from the Walter Reed Army Hospital, the following general reports were noted. The most common alteration in serum proteins were:

1. A depression of serum albumin. This was seen most frequently in chronic wasting diseases, inanition, cirrhosis, malignant disease — particularly wide spread metastatic cancer, and in the various forms of nephrosis.

2. An elevation of alpha 2 globulin. This was seen most frequently in acute infectious or inflammatory states, such as pneumonia, infectious hepatitis, and acute thrombophlebitis.

3. An elevation in gamma globulin. This was noted most frequently in diseases in which one would expect an elevation of antibody titre. It was seen in tuberculosis, sarcoidosis, and in chronic inflammatory diseases of connective tissues such as lupus erythematosis, rheumatoid arthritis and periarteritis nodosum.

Protein patterns seen in most disease states are non-specific. Changes in the serum and plasma proteins usually manifest themselves by increases or decreases in the concentrations of the normal components, or by the appearance of the proteins not seen under normal conditions. These changes can almost be predicted without the electrophoretic analysis, if the common denominators of pathophysiologic conditions are reviewed. Thus, in infectious and inflammatory diseases, the decrease in albumin and increase in globulins have been demonstrated indirectly by the sedimentation rate, variations in the albumin-globulin ratio and by Rouleaux formation.

Some serum proteins are not seen under normal conditions. MUCOPROTEINS are normally occurring proteins which must be isolated at a low pH of 2-4.5. They are present in increased amounts in plasma of patients with pneumonia, bronchogenic and gastric carcinoma, lymphatic leukemia and Hodgkin's disease. CRYOGLOBULINS are characterized by reversible cold precipitation. Electrophoretically, they migrate between beta and gamma globulins. They may be related to Raynaud's syndrome and cold purpura; and are most often—though not commonly—associated with multiple myeloma; and are not diagnostic of any disease. There is no direct relationship between the amount of cryoglobulins, and the presence or severity of symptoms. The electrophoretic pattern of severe macroglobulinemia is indistinguishable from that of

multiple myeloma — this differentiation must be made by ultracentrifuge techniques. Marked macroglobulinemia is frequently associated with a definite syndrome "Waldenstrom's macroglobulinemia" — characterized by dyspnea, mucous membrane bleeding, and bone marrow infiltration of small atypical lymphocytes.

Serum protein values in ambulatory subjects are significantly higher than in patients or normal subjects at bed rest, owing to hemodilution when recumbent, resulting from return into the circulation of edema fluid which collects in the legs on standing. The highest plasma albumin levels occur in healthy subjects. In anorexia nervosa and in volunteers on a starvation diet—the plasma protein concentration and electrophoretic pattern is within normal range.

Each of the five component peaks represents 90-95% of that component, with small amounts of the others. The main limitation of electrophoretic protein analysis is the fact that the separation of protein components depends upon a single property — their mobility in an electric field.

In disease states associated with wasting or malnutrition, serum albumin is lower. It is especially pronounced when there is marked loss of albumin in the urine (nephrotic syndrome), when there is a disturbance in albumin formation (cirrhosis of the liver) or with extravasation of proteins (burns).

The following ten case abstracts illustrate these changes in electrophoretic patterns, and each pattern is given in Table I.

Table I
ELECTROPHORECTIC SERUM PROTEINS

Normal Percentages Mean Average CASE	GAMMA 11-24 (17.5)	BETA 9-19 (13.9)	ALPHA$_2$ 6-14 (9.9)	ALPHA$_1$ 3-8 (5)	ALBUMIN 45-62 (53)	TOTAL PROTEIN 6.3-8 Gm.
1. Nephrosis	16	32	27	6	20	5
2. Diabetic Nephropathy	32	23	38	7	ABSENT	3.1
3. Laennec's Cirrhosis	44	12	8	8	28	5.4
4. Postnecrotic Cirrhosis	50	19	6	3	21	7.4
5. Thrombophlebitis	15	22	19	8	35	6.1
6. Rheumatoid Arthritis	40	14	8	4	34	8.1
7. Infectious Hepatitis	44	12	6	4	33	5.8
8. Carcinomatosis	22	24	17	14	23	3.7
9. Multiple Myeloma	39	13	12	6	30	8.9
10. Hypogammaglobulinemia	4	16	10	6	64	6.3

CASE NO. 1.

The serum was obtained from a five year old white female who had a history of pyelitis at age 2, and was admitted with an 8 month history of periorbital edema. She was found to have 4 plus albuminuria and a few fatty casts. NPN was 35. Hgb. 12.5, WBC 16,150, cholesterol 550. Note here the elevated beta and alpha 2 globulins, with a markedly reduced albumin — a fairly consistent and diagnostic finding in nephrosis. After treatment with ACTH, the serum albumin may rise and the beta and alpha 2 globulins revert to normal concentrations.

CASE NO. 2

A white male, 55 years old, with a five year history of diabetes mellitus. He had been known to have a high renal threshold for glucose, but had been well controlled by 28 units NPH insulin daily. Seven months prior to this serum protein study, he had developed peripheral edema resistant to therapy, and also subsequently pleural effusion and thrombophlebitis involving both legs. There was some question as to exposure to hepatotoxins in connection with his work in sales of cement sealers, disinfectants, etc. Liver biopsy showed fibrosis only, and an iron stain was negative. A renal biopsy yielded only a small piece of tissue and the patient would not allow it to be repeated. NPN 38 mg %. 24 hour urine contained 6 grams of protein. Hgb. 12.8 mg %. Bence Jones protein was absent. An L E test was negative. Note here particularly the elevated gamma and alpha 2 globulins and the total absence of albumin. The percentages here are undoubtedly altered by the markedly abnormal absolute concentrations. In this patient with diabetes mellitus with nephropathy, treatment with salt pure albumin over a one month period of time effected only an elevation of the albumin concentration to 5%.

CASE NO. 3

A 54 year old white male with a liver biopsy diagnosis of Laennec's cirrhosis who was admitted with bronchopneumonia in 1956, and in 1957 with bleeding varices, which eventually led to his demise. Serum bilirubin, total 9 mg %, direct 3 mg %, CO_2 18.3 mg %, BUN 25 mg %, hgb. 11.5 gms %, cephalin cholesterol 4 plus, thymol turbidity 16 units, thymol flocculation 3 plus. Again note the markedly elevated gamma globulin and depressed albumin. Although it is certainly not diagnostic, in two thirds of cirrhotics the gamma globulin is found to be elevated.

CASE NO. 4

The serum was obtained from a 52 year old, obese, white female who had jaundice 12 years ago, followed by evidence of liver disease. Five years ago she had a splenectomy for hepatosplenomegaly, at which time a shunt was not possible due to technical reasons. A liver biopsy at that time revealed postnecrotic cirrhosis. In 1957 she first developed peripheral edema and two months later died with bronchopneumonia and lung abscesses. Note the markedly elevated gamma globulin and depressed albumin again on this patient. On a later study macroglobulins were found to be present by ultracentrifuge study.

CASE NO. 5

This serum was obtained from a 39 year old white male who had thrombocytopenic purpura 12 years ago, followed 7 years ago by a splenectomy. He was admitted with thrombophlebitis. Hgb. 18.5 gms %, WBC 15,450 with an increased number of polymorphonuclears. Platelets 130,000. Note here the moderate increase in the alpha 2 globulins characteristic of infectious states.

CASE NO. 6

Serum was obtained from a 56 year old negro female with painful swelling of her left knee which was diagnosed clinically as rheumatoid arthritis. Bence Jones

protein was negative. Note here the three-fold elevation of the gamma globulin and the moderately depressed albumin.

CASE NO. 7

The serum was obtained from a 30 year old white female who clinically had infectious hepatitis with a two month history of jaundice, malaise, dark urine, light stools and a distaste for cigarettes. She followed a rapid downhill course, terminating in coma and death three weeks after admission. Transaminase 416, bilirubin: total 13 mg %, direct 6 mg %. Alkaline phosphatase 4.4, heterophile negative. Again note the markedly elevated gamma globulin and depressed albumin in this patient with infectious hepatitis.

CASE NO. 8

Electrophoretic pattern of serum obtained from a patient who had had endometrial carcinoma for 2 years with abdominal carcinomatosis for 9 months. Although there is a definite tendency toward lower albumin and elevated alpha 2 globulin in carcinoma and sarcoma, this tendency is largely dependent upon the presence of widespread disease, and probably does not represent a specific abnormality due to the presence of malignancy. Note here that both the alpha 2 and alpha 1 globulins are slightly elevated and the albumin markedly depressed.

CASE NO. 9

The serum was obtained from a 60 year old colored male who had a pyarthrosis of his knee in 1955 when a peripheral blood smear revealed target cells, a left shift, Rouleaux formation, and 1 myelocyte. In 1957 he was found to have a blue mass growing on the lateral tongue margin, a liver 6 cm. below the costal margin and arthritic complaints. A bone marrow aspiration revealed myeloma cells and a diagnosis of multiple myeloma was established. Cryoglobulins were found to be present in his serum. The other findings as noted were a marked elevation of gamma globulin and a depression of the albumin with a high serum protein.

CASE NO. 10

The serum was obtained from a 9 year old negro boy with a long history of septic infections, draining ears, meningitis twice, and pneumonia three times. He has rheumatoid arthritis, has had one eye and his spleen removed. In the past year he has had 5 hospitalizations for infections. Six electrophoretic patterns have been almost identical to this one. A brother is also known to demonstrate a similar protein abnormality. Note here the marked hypogammaglobulinemia. Administration of regular doses of intramuscular gamma globulin has not altered the protein picture in this patient, for the gamma globulin has varied only from 4 to 6%.

Figure 2 touches upon the usefulness of electrophoretic study of the hemoglobins. The first filter paper strip represents 100% "A" hemoglobin, as found in normal adults. In sickle cell anemia, 85 to 100% of the hemoglobin is of the "S" type. The second filter paper strip represents the hemoglobin pattern found in sickle cell trait

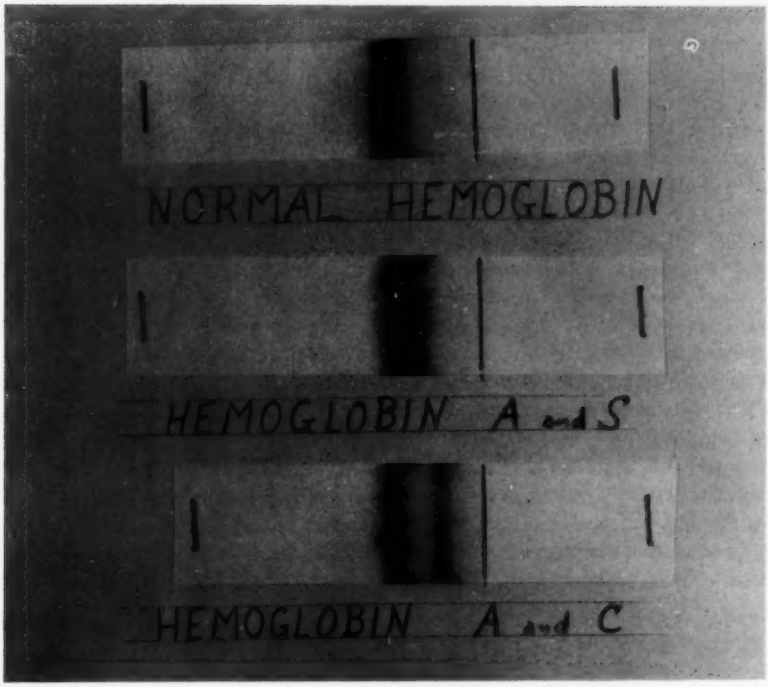

Figure II

Electrophoretic pattern of normal hemoglobin compared with that of hemoglobins S, and C.

in which approximately 35% of the hemoglobin is of the "S" type and 65% is of the "A" type. In hemoglobin "C" disease, 100% of the hemoglobin is of the "C" type. The third filter paper strip represents a mixture of the "A" and "C" types of hemoglobin as seen in a negro child with hemoglobin "C" disease who had received blood transfusions. Thus, we can see that electrophoretic study, while not necessary, is helpful in separating sickle cell trait from sickle cell anemia. It is also of definite value in establishing the diagnosis of hemoglobin "C" disease.

We have tried to point out some of the helpful clinical applications of the electrophoretic protein analysis. As you have seen pointed out on the chart and by the case summaries, many of the alterations are non-specific. The study of protein patterns by electrophoresis is fascinating, is not intended to be a substitute for good clinical judgment, and should be particularly correlated with the physician's own estimate of the patient's status.

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AN ELASTIC ARTERIAL SUBSTITUTE MADE OF DACRON TEXTILE FABRIC

D. Emerick Szilagyi, M.D.* and Lloyd France, M.D.*

The rapid development of vascular surgery during the past ten years was made possible by the revival and perfection of operative techniques that make use of homologous arterial grafts. The versatility and ease of technical handling of arterial homografts as well as the excellence of their early success rate still stand unchallenged. However, observations on the histologic changes in these implants uncovered a serious deficiency.[1,2] Contrary to the expectations of many, homologous arterial grafts share the fate of all homologous tissue transplants, and, instead of being receptively incorporated by the host tissues and reinforced by ingrowth of connective tissues elements, they are as a rule only passively tolerated and occasionally even actively rejected. In either case they may fail. If they are rejected, they may fail early by thrombosis or disruption; if they are sequestrated they gradually lose their structural strength, and often become dilated, tortuous or aneurysmal, in which case they either occlude or, rarely, rupture. In the instance of aortic grafts this process of wearing out may take many years; indeed, in most cases the graft outlives the patient. Femoral arterial grafts, however, show a relatively early as well as a much higher incidence of structural failure.

Ever since the important observation of Voorhees and his associates[3] that the animal body builds a connective tissue channel around a porous textile fabric placed in the path of the flowing blood, the search for arterial substitutes made of plastic materials has been intensive mainly for the reason of the practical advantages that a man-made arterial prosthesis offers. The lack of permanence in the structural strength of arterial homografts just mentioned has lent further urgency to this search. A number of plastics have been investigated by many workers and have gained varying degrees of popularity.

In studying plastic arterial prostheses during the past four years in our laboratory,[4,5] in order to reproduce the hemodynamic conditions of the human arterial sytsem with the greatest practicable fidelity, a canine preparation was used that permits the implantation of arterial substitutes approaching the dimensions of the human femoral artery. In this manner woven seamless prostheses of nylon, dacron and teflon were implanted in groups of dogs. All these postheses showed an excellent rate of early functional success; indeed, the only failures were those caused by technical errors, among which the commonest was inadvertent kinking of the implant. In nonyielding rigid tubes bending results in buckling which inevitably leads to thrombosis. This fault of plastic prostheses had been noted by others but it was particularly conspicuous in these experiments in which the great length of the implants provided frequent occasion for bending. It soon became evident that the ability to elongate and mold—or the quality of elasticity—was a necessary attribute of plastic prostheses if they were to serve in locations where they are apt to be flexed (as they are in almost all clinical situations).

*Division of General Surgery

Since there is no plastic fiber with intrinsic elasticity that would otherwise fulfill the requirements essential for an arterial substitute, we thought of incorporating in the textile fabric a yarn that had been specially processed for resilience. Our first experiment two and a half years ago utilized an elastic prosthesis woven of "Helanca" *nylon,* which then was the only available plastic fiber so processed. The elastic and handling qualities of these prostheses were excellent but their durability was unsatisfactory for use in the replacement of arteries larger than the femoral.

Fourteen months ago a dacron fiber processed with the "Helanca" method came to our notice. Prostheses constructed in a manner similar to that used in making "Helanca" nylon prostheses were then subjected to laboratory investigation.*

The result of these studies will be summarized in the following paragraphs.

Experimental observations. The elastic dacron prosthesis is woven with a taffeta weave and is seamless. As disposed in the tubular fabric, the longitudinal threads forming the warp are made of fibers that have been specially processed; the tranverse threads, or woof or filling, consist of untreated dacron fibers. The special process to which the fibers of the warp yarn have been subjected is the same as that used for the manufacture of "Helanca" nylon fiber. In this process the fibers are twisted into tight spirals and then heat-set at 270° F. Fibers of opposite directions of twist are combined into the yarn in about equal amounts in order to assure balance. The fibers are stretchable since on pull the spirals uncurl; when the pulling force is released the fibers shorten owing to a tendency to resume their heat-set spiral shape. When yarn composed of such fibers is woven into fabric this quality of elasticity is largely retained. It is necessary, however, to boil the fabric in liquid soap to restore complete resiliency. (The contact with soap leaves no deleterious effects provided the fabric is thoroughly rinsed.) The finished tube has an ability to elongate 15-20 percent without deformity (Fig. 1).

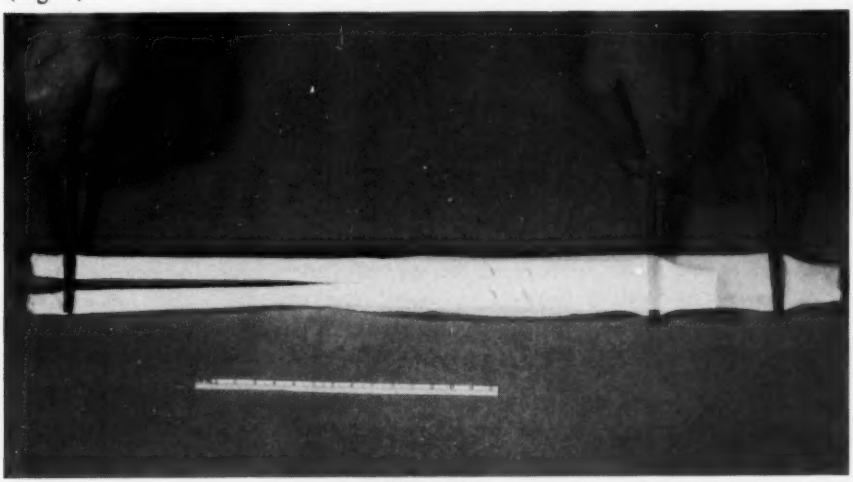

Figure 1

Double exposure of a bifurcation prosthesis showing the range of stretch of the fabric.

*The elastic dacron prosthesis came from the looms of John Sidebotham, Inc., Frankford-Philadelphia, Pennsylvania, whose technical help was essential in its development.

Table 1

Textile Characteristics of Elastic Dacron Prosthesis

Diameter	Ends/cm.	Elastic	Picks/cm.	Filling
mm.	(Warp)	Dacron	(Woof)	(Woof)
10	80 to 100	70/2	47	200

The yarn in the warp: 70 denier 2-ply 70-14 Bright type 51 dacron.

The yarn in the woof: 220 denier 220-50 Bright type 51 dacron.

The textile characteristics of the prostheses used experimentally are given in Table 1. The mesh-size and the weight of the yarn were arrived at after many experimental trials and appeared to fulfill optimally the basic criterion of minimum bulk with maximum strength. The porosity is such that pre-clotting is necessary (see below).

The experimental preparation employed was that first described by McCune and slightly modified by us. The details of the operative technique were given in full in earlier publications.[4,5] Briefly, the procedure consists in implanting a bypass between the upper thoracic and lower abdominal canine aorta, the proximal anastomosis being an end-to-end one, thus assuring a complete shunting of the aortic blood into the prosthesis. The method permits the insertion of implants 18-26 cm. in length and 7-10 cm. in diameter (depending on the size of the animal). We believe that this preparation affords a much more realistic test of a prosthesis than the customary short-segment replacements in many of which the bridging effect of the healing process of the stumps of the host aorta is difficult or impossible to distinguish from the histologic changes peculiar to arteriogenesis. Twenty-one such preparations were made, in 10 of which the prosthesis was implanted with enough slack to allow a tortuous course, thus testing the ability of the prosthesis to mold.

The experimental animals were investigated by observation of their general condition and state of health; by periodic aortograms; and by scheduled sacrifice. The recovered grafts were inspected for gross appearance, tested for tensile strength and studied for histologic characteristics. All the implants remained patent until the death of the animals. In 8 animals that were sacrificed on schedule after periods of time up to 11 months after implantation, and in 5 animals that died of intercurrent causes not related to the function of the implants, the recovered prosthesis showed excellent arteriogenesis (Fig. 2) and a remarkably slight tendency to elicit inflammatory reaction in the host tissues (Fig. 3). During 11 months the tensile strength of the implants remained essentially unchanged in marked contrast to the findings with "Helanca" nylon prostheses in which the tensile strength rapidly declined after two month's implantation (Figs. 4 and 5).

Thus the tubular prosthesis woven with elastic "Helanca" dacron yarn displayed most of the advantageous qualities of the prosthesis made of elastic nylon and, in addition, it appeared to have marked superiority in its durability after implantation; this last property may be looked upon as the result of the marked non-reactivity of dacron yarn.

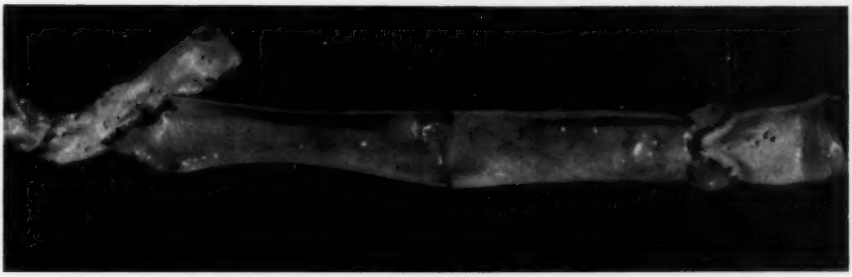

Figure 2

Gross appearance of a canine implant 6 months after insertion. The fabric is completely covered by a smooth flawless psuedo-intima about 1 mm. in thickness. The connective tissue shell and ingrowth are firmly adherent to the fabric and thin but sturdy. The mean total thickness of the new artery is 1.0—1.5 mm.

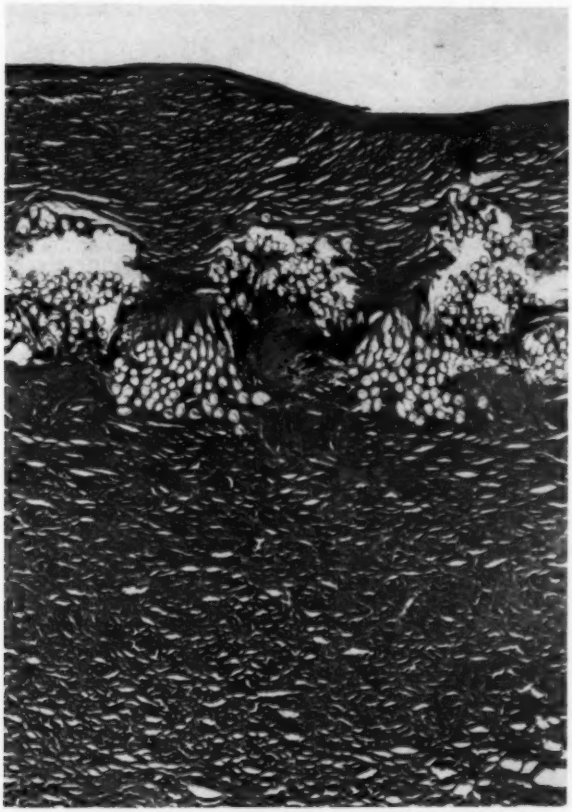

Figure 3

Microscopic section of the mid-portion of implant shown in Figure 2. This is as satisfactory a process of arteriogenesis as we have seen. Cellular exudative reaction is almost completely absent. The growth of connective tissue appears to serve only one purpose: the integration of the plastic fibers into a firm structure. (x70,H.E.Stain.)

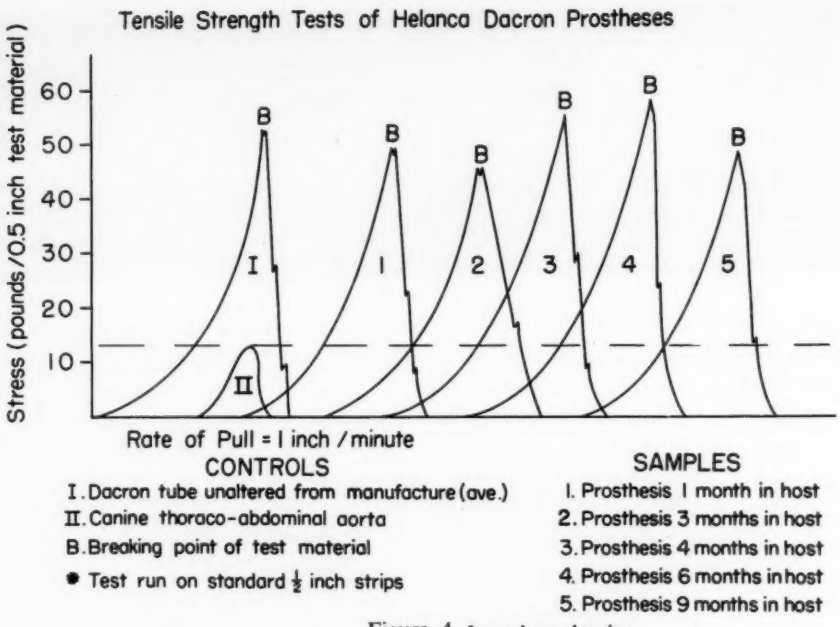

Figure 4 Legend on drawing.

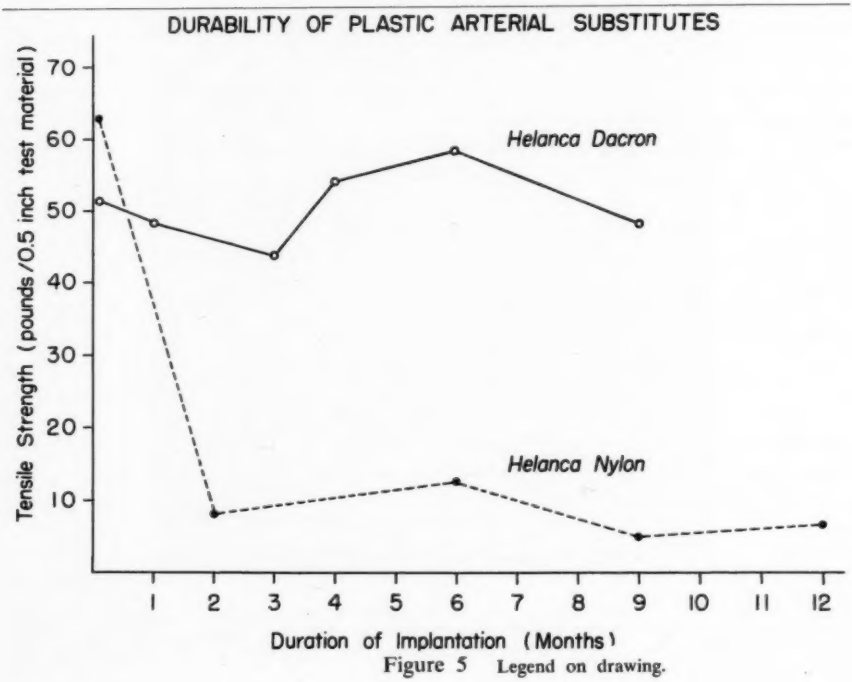

Figure 5 Legend on drawing.

On grounds of these experimental results, in May 1957 we began the clinical use of the elastic dacron prosthesis.

Properties of the Elastic Dacron Prosthesis—The external appearance of the prosthetic tube of stretch dacron as used by us is very similar to that made of stretch nylon. It is white (or, rather, colorless) soft, pliable, smooth, light and moderately porous. On handling it, one is impressed by the lack of bulkiness that is peculiar to knitted or crimped tubes and the absence of stiffness that is characteristic of teflon textiles. The prosthesis does not require any special precautions for storage. It can be sterilized chemically or by boiling and autoclaving. As a sterilizing agent zephiran chloride in 1:1000 solution for 18 hours of contact has been effective. It should be noted that repeated autoclaving reduces elasticity.

Technical details in the clinical use of Elastic Dacron Prosthesis.—Without some appropriate pre-treatment, a fabric of the porosity of the elastic dacron prosthesis will leak blood rather vigorously. We have found that by rinsing the inner and outer surfaces of the prosthesis with 15 to 20 ml of blood obtained from an unherparinized segment of the exposed arterial tree, and by allowing the prosthesis to soak in this blood for 3-4 minutes one can bring about just enough clotting to seal off the meshes of the fabric. A moderate amount of oozing may still occur after the prosthesis has been inserted and blood allowed to flow through it but this can be readily controlled by short periods (20-30 seconds) of occlusion of the inflow while the blood is allowed to remain in the prosthesis. It is of the utmost importance to use great care in the process of clot-sealing. After the in-vitro clotting, the prosthesis must be checked for the presence of visible or palpable thrombi, and if any are found they must be removed by gentle milking or, if necessary, by rinsing with a heparin-saline solution (0.5 mg of heparin per 1.0 ml of saline). The same precaution must be observed during the performance of the insertion of the implant. Obviously, stagnant blood is never allowed to remain in the prosthesis once the clot-sealing has been accomplished. If owing to some technical mishap it becomes necessary to stop the flow of blood through a prosthesis already in place, before the distal clamp is applied the blood is milked out of the implant and the implant is filled with heparin-saline solution until the flow may be re-established. Leaving a layer of thrombus in the lumen of the prosthesis that is thicker than about 0.1-0.2 mm or allowing the presence of lumps of clot may have disastrous consequences. It may not only delay or prevent the orderly formation of the pseudointima, thus resulting in early occlusion, but it may lead to a rapid, almost immediate, progression of the clotting process to a point where the prosthesis cannot function at all.

The free cut end of a woven fabric tends to unravel, particularly if the component yarn contains smooth-surfaced fibers as is the case with the elastic dacron prosthesis. This tendency can be easily corrected, however, by melting and fusing the ends of the cut fibers through the application of heat. We have found it convenient to heat-seal the prosthesis *before* beginning the implantation. The length of the implant is judged by placing a heavy black thread in the exact position the prosthesis is to occupy and by using this measure as the base for the simple calculation. Ten to 15 percent of the length of the thread (depending on the slightly variable elasticity of the plastic tube) is subtracted to obtain the desired dimension. In case of doubt, care is exercised to

make the implant slightly longer rather than shorter than is ideal. The ends of the prosthesis of the desired length are cut with scissors at the angle needed for the proposed anastomosis. The cut ends are lightly touched with a flat-tipped electric cautery which has been heated just short of being red. The ideal heat-seal is a narrow (about 1.0 mm) even and smooth band of fused plastic which lies exactly in line with the scissors cut.

A light touch and attention to technique are necessary for the proficient use of any plastic prosthesis, and they are of special import when dealing with light woven fabrics. The manual handling and the suturing of the elastic dacron prosthesis demand great gentleness. The prosthesis must not be picked up with instruments having a rough surface, and clamps applied to it must be rubber-shod. If, nevertheless, separation of some of the theads occurs, the flaw can usually be corrected by gentle rubbing between fingers. In placing sutures, only the slightest strain is allowed on the fabric.

The optimal size of prosthesis to be used in a given case is a matter of some doubt. Theoretical arguments can be advanced in favor of the use of implants significantly larger in diameter than the host artery and also in favor of reducing the size of the prosthesis. As an empirical proposition, the use of prostheses of approximately the same size as the proximal host artery has appeared to us entirely satisfactory. In the femoral and popliteal areas an upward correction of about 2.0 mm in the inside diameter is made in order to allow for the thickness of the luminal component of the connective tissue conduit to be built by the host.

The technical details enumerated are valid for the straight tubular as well as for the bifurcated prostheses. Because of problems inherent in weaving techniques the undersurface of bifurcations (the so-called "crotch") is not truly seamless. Although we have found that the seal of the weave at the crotch has been consistently strong, it is advisable to inspect this part of the bifurcation prostheses with particular attention before use.

Clinical Material. During the period covered by this report (May 1957 to March 1958) as well as the 12 months immediately preceding it, the criteria governing our choice of direct surgical procedures for occlusive disease and our preference for arterial substitutes favored bypass operations over replacements and plastic substitutes over homografts. Thromboendarteriectomy was used more frequently than before, but always for sharply localized lesions, particularly in the aortoiliac area. The more advanced and diffuse instances of occlusive disease were treated with bypass procedures, bilateral aorto-femoral and long common-femoral-popliteal bypasses having been particularly common. The implant material in the angioplastic procedures was, with very rare exceptions, plastic tubing.

The advanced state of the disease in the cases chosen for grafting, and the frequent use of bilateral aorto-femoral and of the long femoro-popliteal bypasses emphasize the severity of the test to which the elastic dacron prosthesis was put in this clinical series. Both these operations are rather complex, and they demand a tortuous placement of the implant; moreover, in the femoro-popliteal bypasses the length of the prosthesis is great (without exception in excess of 31.0 cm), a circumstance that—other factors being equal—is unfavorable to patency in an arterial replacement.

Elastic Arterial Substitute

The immediate and early results of the operations in which elastic dacron prosthesis was used are listed in Table 2. The postoperative periods of observation in these cases ranged from 1 to 12 months. Patency of the graft was always verified by angiography. The results tabulated are cumulative. "Immediate result" denotes the state of the implant at the time of discharge from the hospital; "early result" refers to the condition of the implant at the time of the last angiographic examination. Clinical examinations were made monthly. The results are slightly inferior to those we have generally observed with the use of homografts. This difference can be largely explained by the selectivity of the case material; as pointed out above, an unduly great proportion of the cases in which elastic dacron prostheses were used were examples of advanced disease. The initial lack of familiarity with the new fabric may also well have contributed to the lesser success. It seems probable, however, that the early results of operations using homografts cannot be matched, much less surpassed, by procedures with plastic prostheses. The superiority of plastic substitutes lies in the long-range outlook, that is, in the hope that the good early results will remain good late results in a significantly larger proportion of cases than after homografting.

Table 2

Results of Elastic Dacron Grafting Procedures — May 1957 — April 1958

	Immediate		Early	
	Open	Closed	Open	Closed
Aorto-iliac	30	3	30	3
	91%	9%	91%	9%
Femoro-Popliteal	23	5	20	8
	82%	18%	72%	28%
Total	53	8	50	11
	87%	13%	82%	18%

The prosthetic qualities of elastic dacron tubes. It is our belief that a plastic prosthesis suitable for wide-range clinical use that will yield the best results must combine the following qualities: It must be seamless, smooth-walled, easy to handle, durable and relatively non-reactive; its porosity and bulk must meet certain critical requirements; and finally it must possess the ability to elongate and recoil. (Further important but not truly essential requirements for such a prosthesis would be economical cost, easy storage and simplicity of sterilization.)

The reasons for the significance of these attributes are cogent. The presence of a seam and of ridges on the luminal surface of the prosthesis is undesirable since surface irregularities would increase friction and, therefore, resistance to flow; moreover, and perhaps more importantly, they would promote excessive clotting along the areas of contact with the blood, a circumstance that, under many marginal conditions, may mean the difference between patency and thrombotic occlusion. The need for ease of handling (as well as for less essential factors of low cost and simplicity of storage and sterilization) is self-evident. Durability is also an obvious requirement. It is less obvious that durability is largely dependent on lack of tissue reactivity. Regardless of the magnitude

of tensile strength that the original fabric possesses, if after implantation the fabric provokes active cellular reaction in the host tissues it will be attacked by the exudative process, and in the end, partly or completely destroyed. The optimal degree of porosity in the fabric is the sum of two requirements: the mesh size must be large enough to allow ingress for the ingrowth of connective tissue but it must also be small enough not to interfere with hemostasis. The restrictions on the bulk (or wall thickness) of the prosthesis are less easy to justify. Undoubtedly thick-walled, heavy prostheses have served well in many situations during short-term observations. However, a plastic prosthesis is a foreign body, and sound surgical principles would suggest that its mass should be kept to a minimum as long as this restriction does not result in a disadvantage such as lessening its initial tensile strength or its durability. While conclusive evidence condemning thick-walled prostheses cannot at this time be quoted, it is an easily confirmed observation that the connective tissue reaction around bulky prostheses is excessive, and this is undesirable. The importance of the quality of elasticity has already been discussed. It may be mentioned, however, that the accomplishment of elasticity through specially treated fibers has distinct advantages over methods involving the treatment of the finished tube, namely, crimping, which increases bulk and luminal friction.

While far from ideal, the elastic dacron prosthesis comes reasonably close to meeting the requirements just enumerated. Its construction is light, seamless and smooth-walled, providing a porosity that is satisfactory both from the point of view of arteriogenesis and from that of hemostasis. Its tissue reactivity is of the order of that of teflon, and during the period of experimental observation its tensile strength has remained remarkably stable. It also meets the other prerequisites mentioned that have less fundamental importance but are significant in a practical way.

Some imperfections of the elastic dacron prosthesis should, however, be pointed out. There is some experimental and clinical evidence that the new-formed lining of the prosthesis is slow to develop, apparently slower than that seen in nylon implants. Since the formation of this pseudointima is greatly influenced by the technique of pre-clotting which is largely a matter of personal skill, the evidence in this regard is not entirely clear-cut or convincing. Moreover, it is reassuring that in older canine specimens the new intima was always found to be satisfactory and in most instances excellent. Because of the delay in the formation of the new lining, angiographic visualization of the prosthesis should be delayed until at least the sixth postoperative week.—The other shortcoming of the prosthesis is troublesome rather than grave, and it consists in the tendency of the component threads of the fabric to slip and separate. Measures—chief of which is gentleness in handling—have been mentioned to prevent this mishap or to correct its consequences. This imperfection is to large extent a manufacturing problem. Studies are now in progress to prevent its occurrence by using in the woof a dacron yarn of different finish and much greater cohesion.

*It should be borne in mind that elasticity has very little, if anything to do with the physiological function of the plastic prosthesis. The prosthesis must be able to elongate and recoil not because of the requirements of pulsatile flow but because of the need to accommodate itself to the anatomical features of its surrounding. Once the implant has become fixed in its optimal anatomical position this need ceases to exist. As a matter of fact, the ingrowth of connective tissue does dissipate the elastic quality, and after 2 to 3 months following implantation in the dog the prosthesis is found to be quite rigid.

SUMMARY

An account is given of the experimental and clinical findings in the use of an arterial substitute, woven of dacron yarn, which is seamless, smooth-walled, finely porous, light, and has elastic qualities.

In animal experiments, during 14 months of observation, the prosthesis showed low tissue reactivity, good arteriogenesis and excellent durability.

Used as direct replacement and as bypass graft in the aorto-iliac and femoro-popliteal areas, in 61 clinical cases (the earliest of which has been followed for 12 months) the prosthesis has yielded patency rates only slightly lower than those obtained by us with homografts. Further observation is needed to show whether the use of this prosthesis will reduce the rate of late failures due to degenerative changes noted in homologous arterial transplants.

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SOFT TISSUE NECROSIS DUE TO NOREPINEPHRINE INFUSIONS

ALEX P. KELLY, JR., M.D.*

A number of cases have been reported in recent years of skin slough secondary to the intravenous administration of norepinephrine. This complication is not infrequent in patients receiving this drug. The mortality of those receiving more than minimal dosage is sufficiently high to prevent the complication from becoming apparent in many instances. The necrosis can be heroic in proportions and the morbidity several times that of the condition being treated.

The earlier reports in the literature were concerned with known extravasation at the infusion site. It was felt that careful insertion of a polyethylene catheter well into the vein would obviate the danger of necrosis.

It was soon apparent that insertion of the catheter atraumatically well into the vein was no protection against necrosis. Necrosis has been noted 20 centimeters proximal to the catheter tip.[1] Impure drugs were considered also, but this was ruled out by several lots of the drugs behaving in a similar manner.[2]

It is now apparent that ischemia in the superficial soft tissue of the extremity being used for the infusion is a risk inherent in the use of norepinephrine. Close has suggested the use of a catheter inserted through a high saphenous phlebostomy into the iliac vein as a method of avoiding necrosis.[3] The immediate dilution of the infusion and adequate blood flow certainly should offer maximal protection against complications.

Several cases have been seen by plastic surgery service in consultation and are recounted briefly below.

CASE #1 — A.B. — A 52 year old white female admitted with pyelonephritis and lithiasis in her only kidney. She was anuric. NPN was 148 mg%; B.P. 80/60. Norepinephrine 8 meg/per cc. was started through a polyethylene catheter inserted in an ankle cutdown, and continued for 24 hours. Therapeutic response was good. No gross extravasation was noted. At the end of 48 hours reddened areas were noted in the anterior tibial areas at level of the catheter tip. Over the next four days these areas slowly demarcated. The necrotic areas were debrided and split thickness skin grafts applied 26 days after admission. The take of the grafts was moderately good. Several small unhealed areas remained which healed within the month after discharge.

CASE #2 — T.S. — A 51 year old white male with advanced multiple sclerosis admitted unconscious and areflexic to the Emergency Room. Norepinephrine 8 mcg. per cc. was administered intravenously through an ankle cutdown, and continued for 36 hours. At this time edema and pallor were noted above the cutdown. This was followed by redness and bleb formation progressing to a purplish hue over the next 48 hours. The wounds were debrided under general anesthesia, 18 days after admission and split thickness skin grafts applied. The grafts healed well except over a small area of exposed tibia. The exposed bone was removed and the area healed without further therapy.

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Figure I, Case I
Tissue injury and necrosis from intravenous norepinephrine.

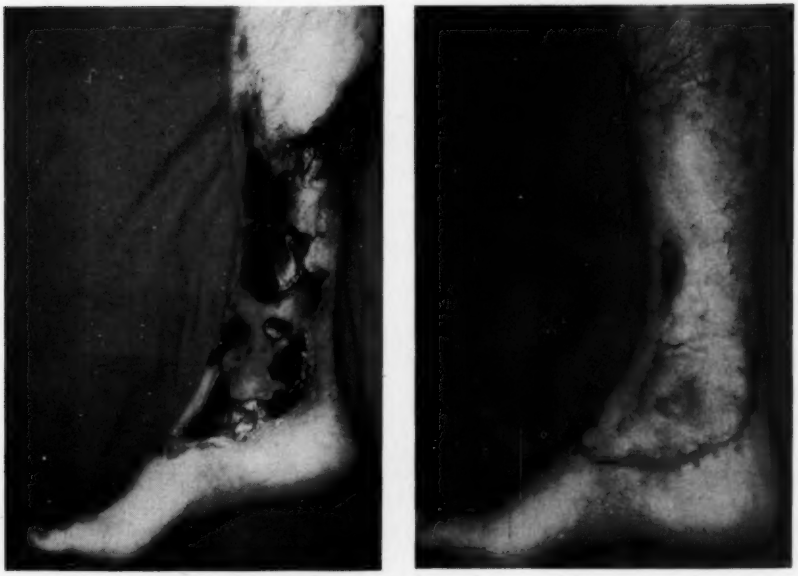

Figure II, Case II
Necrosis, left, and repair by skin graft, right.

CASE #3 — D. J. — A 60 year old colored male admitted with asthmatic bronchitis. On the day following admission he developed an acute vasomotor collapse, presumably from iodide sensitivity. Blood pressure was 60/0. Norepinephrine 4 mcg. per cc. was started in an arm vein and a satisfactory response obtained. The patient removed the IV needle at the end of 24 hours and his pressure promptly fell to 68/0. The norepinephrine infusion was started in the opposite arm and continued for an additional 24 hours. Superficial blistering developed in 24 hours and slowly progressed to dry gangrene of both antecubital areas. One month after admission the sloughs were excised under local anesthesia and split thickness skin grafts applied. The healing of the grafts was poor. Necrotic areas were debrided and healing obtained by application of stored autogenous skin grafts.

Figure III, Case III

Necrosis of areas of skin of both arms from intravenous norepinephrine.

CASE #4 — H. M. — A 64 year old white female admitted with cholecystitis and lithiasis, critically ill. Her condition steadily worsened with onset of congestive failure and unconsciousness. Started on Norephinephrine which was given 8 meg/cc over a 12 hours period. Difficulty was experienced with extravasation and the cutdown had to be restarted. Necrosis was noted first as an annular blistering with an apparently viable center portion about 4 x 6 cm. Because of her precarious general condition due to recurrent bouts of pancreatitis, it was felt surgical treatment of the necrotic area should be deferred. Debridement was carried out on the ward piecemeal and the patient discharged with an unhealed lower leg ulcer. After one year the ulcer had not healed. The patient was then re-admitted and the ulcer closed by split thickness skin grafts.

Figure IV, Case IV
Necrosis from intravenous norepinephrine.

CASE #5 — M.P. — A 34 year old colored female seen in the Emergency Room with a lacerated extensor tendon of the hand. After careful questioning she was given an intramuscular dose of penicillin. She collapsed within a few minutes. Blood pressure was 40/0. Intravenous Benedryl and Cortisone were administered with a satisfactory immediate response. Norepinephrine 4 meg. per cc. was given by infusion into the antecubital vein. Eight hours later the infusion was found to have infiltrated into the tissues. The arm and forearm were edematous and markedly cold. It was felt that this patient would surely develop necrosis. 50 cc. of xyocaine 1% and 1500 units of Hyaluronidase were infiltrated into the area of extravasation. The swelling and ischemia were alleviated and progress from this point was uneventful.

Treatment

The treatment of the manifest necrotic area is not materially different from sloughs secondary to a number of other therapeutic or physical agents. Debridement of the necrotic skin is accomplished under suitable anesthetic. The precarious general state of some of these patients necessitates the use of local anesthesia. The fat necrosis often extends beneath viable skin, especially along the course of blood vessels. It may be necessary to delay the application of skin grafts for several days if there is any doubt as to the adequacy of the debridement.

It is naturally desirable to initiate treatment which will prevent the onset of necrosis. The treatment of choice if extravasation is noted is the infiltration of regitine 5 to 10 mg. in 15 cc. of diluent into the extravasated area[3,4,5]. There may be reluctance

on the part of physician treating the patient to risk giving a therapeutic antagonist which may cause a return of the hypotension he has been vigorously combatting. We would suggest that if the extravasation is recognized early that xylocaine and hyaluronidase be infiltrated into the involved area and if improvement is noted, further treatment can be withheld. The use of hyaluronidase alone has been shown to be ineffective except to reduce the swelling. In the patient who is well stabilized, however, regitine is preferable to other agents. Warm applications to relieve the vasospasm carry a high risk of enhancing the amount of necrosis by increasing the metabolic demands of the ischemic tissue. histamine and mecholyl iontophoresis have been recommended but seem to be unduly involved.[6,7] Allowing spontaneous separation of the slough and healing to take place may take months as illustrated by Case #4. During this prolonged period of healing, a portal is open to potentially dangerous infection.

Discussion

The use of Norepinephrine as a life saving measure in hypotension in spite of its propensity to cause soft tissue necrosis can be stoutly defended. Its prolonged usage to the exclusion of proper blood volume or electrolyte replacement or correction of cardio respiratory inbalances, and its use for less emergent hypotensive states, may place the physician in an untenable position if tissue necrosis ensues.

Conclusions

Norepinephrine causes profound ischemia of the tissues surrounding the vessel into which it is introduced. This is due to extravasation of the Norepinephrine into the surrounding tissues. It is not dependent on gross leakage from the vessel at the infusion site. This extravasation is apparently enhanced by increased capillary permeability associated with hyoptensive states.

It is incumbent upon the physician to observe the infusion sites and areas between the infusion and major venous channels at frequent intervals during therapy. Ischemia can be noted early and treatment can be instituted if feasible or notations made in the record why treatment is being deferred.

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SEVERE HYPERBILIRUBINEMIA DUE TO BENIGN OBSTRUCTION OF THE COMMON BILE DUCT

CASE REPORT

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Icterus always presents an interesting problem of differential diagnosis. The "usual task is to determine whether jaundice is due to primary liver disease or to obstruction of the extrahepatic bile ducts by stone or tumor"[1]. The patient in this case report presented an unusual problem because of a remarkably high total serum bilirubin of 53 mg. per 100 cc. Bockus[2] states that the bilirubin rarely exceeds 10 mg. per 100 cc. of serum if the jaundice is associated with gallstones. When a neoplasm causes biliary obstruction, the bilirubinemia rises steadily to between 20 and 30 mg. per 100 cc. in most patients. In fatal viral hepatitis the jaundice may be extreme. The serum bilirubin concentration in our patient was the highest we have seen from any cause. Inasmuch as the etiology was benign, we are presenting this case report as an interesting exercise in differential diagnosis.

CASE REPORT

A 56 year old negro male was admitted to the hospital in October, 1956 with jaundice of four days duration. He had been seen regularly as an outpatient for fifteen years. In 1946, he had been hospitalized during an episode of transient jaundice with a provisional diagnosis of viral hepatitis. A review of the 1946 record does not confirm the etiology of his icterus at that time. He had been anorexic with chills and fever to 103 defrees Fahrenheit. He had been under treatment for prostatitis and was an alcoholic. In 1946, his cephalin cholesterol flocculation was four plus, thymol turbidity 4 units, and thymol flocculation negative. The leucocyte count was 7,900 per cu. ml., with 95 per cent polymorphonuclears. Cold agglutination determinations had been negative. His icteric index had elevated to 15 and the bromsulfalein retention was 19 per cent in forty-five minutes. The oral hippuric acid test was normal.

During the following ten years the patient had annual liver function studies. The forty-five minute bromsulfalein retention varied from 6 to 12 per cent. The cephalin cholesterol flocculation remained negative. The thymol turbidity was 8 units in 1949, but usually was below 4 units; and the thymol flocculation varied from negative to four plus. Abnormal liver function tests during this ten year period seemed to correlate with his intemperate use of alcohol. A right inguinal herniorrhaphy was performed in 1951, at which time there was no hepatomegaly.

One day prior to the present admission, the patient had been seen as an outpatient complaining of nausea and vomiting. The gallbladder was palpable and tender, and his sclerae were icteric. There had been a recent alcoholic debauch. He had not taken any medications and there had been no transfusions or needle injections. After the initial examination the gallbladder was not palpable, but the liver was felt 3 cm. below the right costal margin. The patient was able to eat most of his food, but his

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appetite was easily satiated. He had no chills and no fever.

The initial laboratory studies revealed a total serum bilirubin of 7 mg. per 100 cc. with a direct reacting bilirubin of 4.2 mg. per 100 cc. The urinanalysis was within normal limits. The hemoglobin was 14.1 gm. per 100 cc., leucocyte count 8,250 per cu. ml., polymorpho-neutrophiles 74, eosinophiles 4, lymphocytes 19, monocytes 3. The serum cholesterol was 222 mg. per 100 cc., with a 38 per cent ester fraction. The fasting blood sugar was 100 mg. per 100 cc., non-protein nitrogen 34 mg. per 100 cc. The serum alkaline phosphatase was 7 units and the prothrombin time 15 seconds (100 per cent). The transaminase was 22 and the serum iron 164 micrograms. His cephalin cholesterol was four plus, thymol turbidity 2 units, and the thymol flocculation one plus. The patient's stool gave a strong reaction for bile by the Schmidt test. In the transduodenal biliary drainage, microscopic stones and calcium bilirubinate pigment were seen in the "B" bile fraction. The "A" and "C" bile fractions were clear. His fasting gastric acidity was 8 degrees; the maximum free acidity being 64 degrees after a stimulating test meal.

During the first ten days in the hospital, the patient's bilirubin decreased to 5 mg. per 100 cc. The bile reaction in the stool remained strongly positive. A needle biopsy of the liver was done on the seventh hospital day. This revealed bile stasis with acute and chronic cholangitis. On the eleventh hospital day the patient was more icteric and the serum bilirubin had elevated to 31.6 mg. per 100 cc. with a direct reacting bilirubin of 15.6 mg, per 100 cc. The serum cholesterol was 262 mg. per 100 cc., and the alkaline phosphatase had risen to 26.4 units. The thymol turbidity had increased to 8 units. The quantitative urinary urobilinogen, which had been 0.8 units on admission, had now become elevated to 5.8 units per 100 cc.

The patient's icterus increased and on the twentieth hospital day the stool became negative for the presence of bile for the first time. The serum bilirubin was remarkably high. By dilution techniques it was determined to be 53 mg. per 100 cc. with 32 mg. of direct reacting bilirubin. At this time no bile was obtained by transduodenal drainage. The alkaline phosphatase was 31.8 units. A sickle test was negative. The leucocyte count was 12,450 per cu. ml., with 82 per cent polymorpho-neutrophiles. By serum electrophoresis the total protein was 7.2 gm. per 100 cc., gamma globulin 22, betta globulin 24, alpha 1 globulin 10, alpha 2 globulin 6, and serum albumin 39 per cent.

No calcification had been seen in a scout film of the abdomen at the time of admission. A roentgenologic study of the stomach and duodenal loop had been normal.

The differential diagnosis had included the possibility of hepatitis during the first three weeks of observation. Although the patient's liver flocculation studies were not greatly abnormal, the serum iron had elevated and the urinary urobilogen was increased. After the elevation of serum alkaline phosphatase and a rise in temperature to 100.5 degrees Fahrenheit, indicating the presence of obstructive jaundice with cholangitis, the need for surgery was evident.

Surgery was carried out on the twenty-first day. The liver was enlarged and deeply pigmented, but not necrotic. The omentum was adherent to the gallbladder, which showed mild distention. The common bile duct was dilated, and a stone could be felt

within its lumen. The duct was then opened, and was found to be filled with thick, inspissated bile. One stone approximately 1 cm. in diameter, and a number of very small stones were removed from the lower end of the common bile duct. The sphincter of Oddi was very stenotic. It was dilated with dilators to seven millimeters. The bile ducts were then irrigated thoroughly and golden bile appeared from the liver. There was no evidence of a malignant lesion in the pancreas or the ampullary region of the common bile duct. The gallbladder was opened and thoroughly irrigated. It did not contain stones, although it appeared that several small stones were flushed from the cystic duct. A T-tube was placed in the common bile duct, and a cholecystojejunostomy was performed.

The patient's postoperative convalescence was satisfactory. The jaundice cleared slowly. Cholangiograms made via the T-tube showed no abnormalities, other than the residual dilatation of the common bile duct. The media flowed freely into the duodenum. The T-tube was removed and the patient has remained well. There has been no icterus during the past year.

DISCUSSION

Early in the patient's illness the differentiation of obstructive jaundice from hepatocellular disease was not obvious. A prior viral hepatitis was not clearly proved. The normal bile reaction in the stool, a normal quantitative urinary urobilinogen, and absence of a alkaline phosphatase retention did not conform to the criteria for extrahepatic obstruction. The positive flocculation tests, the elevated serum iron, and the rise in urinary urobilinogen prevented an early exclusion of viral hepatitis. An improvement in the icterus during the first week of illness gave caution to surgical intervention. The later excessive elevation in serum bilirubin raised doubts of a possible benign etiology. Considerations of the pathogenesis and final diagnosis in this patient led to interesting speculations.

There are several factors to consider in evaluating hyperbilirubinamia. First, it must be recalled that bile pigment is formed from the disintegration of erythrocytes and more specifically the breakdown of hemoglobin by the reticulo-endothelial system[3,4]. The bile pigment, therefore, is formed largely outside the liver[5]. The degree of bilirubinemia will depend for the most part on:

1. The rate and degree of hemoglobin breakdown.
2. The urinary excretion rate of bilirubin. The normal renal threshold for bilirubin retention in serum is 1.5 to 2.0 mg. per 100 cc.
3. The degree of severity of liver damage or bile duct obstruction causing diminished excretion of bilirubin.

Thus, in complete obstruction of the extrahepatic bile ducts, the intensity of jaundice depends on the degree of hemoglobin wastage and rate of excretion of bile in the urine[6]. With loss of blood the intensity of icterus may decrease; but if the rate of blood destruction increases, as by hemolytic agents, icterus increases. An equilibrium between these various factors is reached and the level of hyperbilirubinemia stabilizes.

Extremely high levels of serum hilirubin have been reported in a few patients with liver atrophy or complete obstruction of the bile ducts. Kuwayte and associates[7] reported a total serum bilirubin of 152.7 mg. per 100 cc. in a patient having a carcinoma at the juncture of the cystic and common hepatic ducts. Bollman[8] has shown two

pigments that react directly with the van den Bergh reagent. One pigment predominates after uncomplicated obstruction of the bile duct. The second pigment appears in larger amounts if biliary obstruction continues. This is due probably to failure of the conversion of the first pigment to the second type if the hepatic cells are diseased. The high value of urinary uroblinogen in our patient indicates some impairment of the excretory function of the liver cells.

The complete biliary obstruction which occurred in the patient presented is thought to have been due to several causes: fibrosis of the sphincter of Oddi, stones in the common bile duct, and inspissation of bile in the bile ducts. Brush, et al[9,10] have emphasized organic structure of the sphincter of Oddi as a primary cause of the statsis and infection which leads to formation of biliary calculi. The sudden rise of the serum bilirubin to an unusually high level may have occurred when the bile in the ducts thickened or an inflammation caused edema of the common bile duct. Prior to the sudden rise, the serum bilirubin level was approximately that expected for obstruction due to stones in the bile ducts. To speculate further, an increase in hemoglobin breakdown may have occurred. Hanger[11] has outlined many of the baffling problems related to obstructive jaundice. Why serum bilirubin does not continue to rise with complete obstructive jaundice is not explained by its elimination through the kidneys. The extremely high serum bilirubin concentration in this patient serves to emphasize the need for further experimental investigation to understand the fate of bilirubin and its derivatives.

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PARKINSONISM: NEUROLOGICAL CONSIDERATIONS

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In this discussion we shall concern ourselves with: 1. a brief review of current theories on the genesis and maintenance of alternating tremor and rigidity; 2. the clinical features of Parkinsonism with attention to *early* symptoms and signs; and 3. the medical treatment, including some comments of clinical interest on the chemistry and pharmacology of anti-Parkinson drugs. Modern surgical methods of treatment (chemopallidolysis, etc.) will not be considered in this paper.

A. The Pathophysiology of Parkinsonism

Whatever the type of Parkinsonism (v. i.), the hallmark of the syndrome is rest tremor and/or rigidity; in fact, some have contended that this pervading rigidity is the basis of almost all other disorders of movement in Parkinsonism—to wit, the abnormalities of gait and posture, the diminished rate and frequency of movement, etc. Now, the exact neural mechanism responsible for the origin and persistence of this rigidity and tremor remains one of the major mysteries of this syndrome. In other words, we still think of Parkinsonism as a classic example of so-called basal ganglia disease; and rightly so, in that the pathology, at least, is concentrated primarily in the substantia nigra and globus pallidus, less consistently in the striatum, and even less conspicuously in the red nucleus, all of which are definite constitutents of the basal ganglia. But, though we know *where* lesions are common, we do not know exactly *how* these particular lesions so disturb the normally smooth functioning of interdependent pyramidal and extrapyramidal systems as to produce alternating tremor and rigidity, the two cardinal symptoms and signs. Theories, evolved from the facts of pathologic anatomy and physiology in humans and in experimental animals, have generally pointed to the tremor and rigidity as 'release' phenomena, a loss of modulation, the result of a break in the "chain of (motor) command", as it were. Despite general acceptance of this 'release' concept, however, there are differences of opinion on exactly what is released. For example, Bucy interprets the globus pallidus lesions as a break in the "chain of command" from cortical suppressor area 4S to primary motor area 4—in other words, he bases his theory on the presumed normal regulatory influence of suppressor area 4S on motor area 4 by way of the suppressor circuit running from 4S to caudate nucleus, then to the globus pallidus, then to the thalamus (ventro-lateral nucleus), then back to area 4; thus when the globus pallidus link is damaged as in Parkinsonism, the suppressor circuit chain is broken, and tremor (and rigidity) result from the unsuppressed pyramidal outflow from area 4. On the other hand, Jenkner and Ward[7] and Falkerts and Spiegel[6] on the basis of experimental work on animals (both stimulation and destruction experiments on the reticular formation in the mid-brain tegmentum) feel that the globus pallidus (and substantia nigra) lesions release other normally subservient nuclear groups in the brain stem reticular formation from pallidal and nigral control, giving free rein to these other nuclear groups which give rise to the reticulo-spinal tract, the extrapyramidal system's major 'voice' in influencing lower motor neurone activity at all spinal levels. Thus, Bucy sees all this as a break in

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suppressor circuit influence on *pyramidal* outflow while other investigators see it as a break in pallidal and nigral control of downstream (reticulospinal) *extrapyramidal* outflow. In this setting of conflicting views and unproven theories, the basic pathophysiology is still to be explained.

The most recent ray of hope for better understanding of this tremor-rigidity problem is the work of Granit[8] who points out that not only the upper motor neurone (both pyramidal and extra pyramidal components) but also the lower motor neurone plays an important role in regulating muscle tone. This lower motor neurone mechanism, the so-called gamma loop, is a "feed-back" or "servo-system", originating in the small gamma anterior horn cells which innervate the muscle spindle fibers; innervated, these fibers contract and, by stretching the sense organ in the spindle, set up afferent stimuli to the large alpha anterior horn cells which innervate the started muscles and hence directly influence their tone and movement, disorders of which characterize Parkinsonism. Thus, from Granit's work it is clear that the alpha anterior horn cells can be driven indirectly through the gamma loop to the spindles as well as directly by other pathways covering upon the alphas. This all ties in, in theory at least, with the role of the central neural mechanisms described above in that the gamma system appears to be activated particularly by the brain stem reticular formation (extrapyramidal) and the alpha cells to be activated by the pyramidal tract. At this time, it is fair to say that this very recent addition to our knowledge of the control of movement is still too young to have borne definite clinical 'fruit'.

B. The Clinical Features of Parkinsonism

Whereas the inner workings of this syndrome remain an enigma, the outer trappings of the advanced stage, at least, are familiar to everyone. The combination of rest tremor, rigidity, poverty and inertia of movement, the loss of associated and expressional movements of arms and face; the masked facies and monotonous speech; the drooling; the shuffling or festinating gait—this is, unmistakably, advanced Parkinsonism. There is no problem in diagnosis here except in our attempt to categorize further as: idiopathic, post-encephalitic, or arteriosclerotic. Despite arguments to the contrary, in practice this can be difficult. With a history of encephalitis, of insidious onset of rigidity first and foremost, of oculo-gyric crises, of drowsiness, and of deficits in convergence and accommodation, a diagnosis of post-encephalitic type is justified; but, in my experience this is *not* a common happenstance. If, on the other hand, the patient is in the fifth or sixth decade and notices rather sudden onset of the characteristic tremor, followed by the other signs described previously, then a diagnosis of idiopathic type would be reasonable; this, by the way, is the type that Parkinson described in his 1817 Essay On The Shaking Palsy (or Paralysis Agitans). Finally, if the patient is in his seventh or eighth decade, is coincidentally hypertensive with mild to moderate dementia and possibly some pseudobulbar symptoms, and develops rigidity insidiously, then the arteriosclerotic type is probable.

The *early* Parkinsonism of insidious onset can be missed, especially in patients in the third to fifth decades, unless we pay particular attention to their complaints of stiffness or heaviness of the arms and legs, weakness or slowness, fatigability and muscle cramps or, even more obscurely, "deadness or numbness" of the arms and legs. In the

setting of these complaints, we must recognize the significance of our findings of reduced frequency of lid-blinking, failure of one or both arms to swing automatically when the patient walks, rigidity in the *proximal* joints (shoulder and hip), difficulty with the rapid rhythmic alternating movements of fingers and hands, the tendency for handwriting to get smaller and smaller the longer the patient writes at one sitting. There is also a so-called "spiked knuckles" sign, indicating the relative prominence of the metacarpophalangeal joints due to the dominance of finger flexor tendon tone over extensor tendon tone in early Parkinsonism. It is also important to recognize that unilateral involvement of the face, arm, and leg in these early cases is common and constitutes the so-called hemi-Parkinsonism. Even in these early cases, the slowness or inertia in the beginnings and endings of movements may be brought out and easily seen when the patient attempts a 90 degree or, particularly, a 180 degree turn while walking; in so doing, the rate of leg movement is conspicuously slowed and the rhythm disturbed until straight-line walking is again attained.

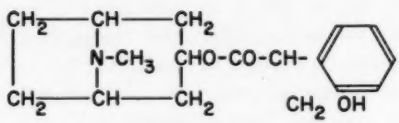
In the differential diagnosis, rarely an intracranial tumor, primary or metastatic, in the neighborhood of the basal ganglia may mimic the clinical picture described, particularly the hemi-Parkinsonism.

C. The Medical Treatment of Parkinsonism

The total care of these patients has three major aspects—1. pharmaceutical; 2. physiotherapeutic; 3. psychiatric. For the most part those of us in office practice lean heavily on the first of these and take care of the second and third needs by urging and helping the patient to seek new channels of expression, at both physical and verbal levels, during every visit to our office. The special skills of physiatrist or psychiatrist may and should be sought when indicated, of course. Physiotherapy, for example, has something to offer in posture-correction, gait-training, muscle-stretching, progressive resistive exercises, and occupational therapy.

The treatment of Parkinsonism is symptomatic, of course, since the underlying neural mechanisms are still not understood. The major symptoms treated are, of course, tremor and rigidity with all their by-products.

There is an already abundant but ever-increasing supply of pharmaceuticals of value in treating Parkinsonism, but they all come under the heading of four main drug groups—namely, *potato plant products and derivatives* (the solanaceous alkaloids); the *synthetic anti-spasmodics;* the *synthetic anti-histaminics;* the *synthetic cerebral stimulants*. The potato plant products which include Atropine, Hyoscine, Hyoscyamine, Stramonium, Belladonna, and Rabellon are the time-honored medicaments for Parkinsonism (Charcot refers to the use of Belladonna and Hyoscyamine in his 1877 text on diseases of the nervous sytem); these are still of definite value. In about the last 15 years the synthetic products mentioned above have become available. The best of the anti-spasmodics have included Artane, Pagitane, and Cogentin. The antihistaminics in common use have included Benadryl and Thephorin and the synthetic cerebral stimulants (Dexedrine and Benzedrine) have found some use in the specific treatment of the lethargy and akinesia of Parkinsonism.



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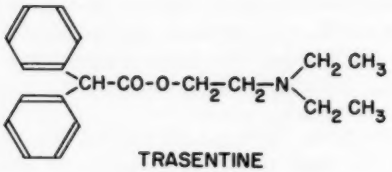

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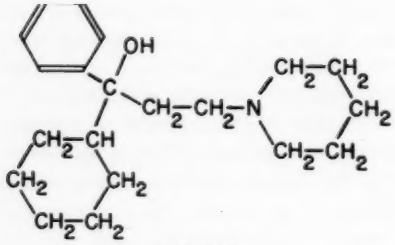

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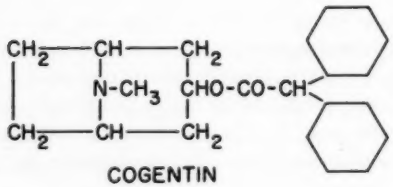

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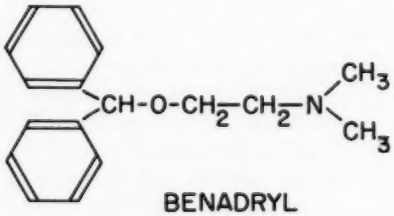

BENADRYL

Figure 1

Structural formulas of some anti-Parkinson drugs; note similarities (see text).

A few general rules should be remembered in the use of these agents: 1. Caution in dosage with any of these drugs in the older patients; heavy dosage may lead to excessive drowsiness or excitement, confusion or hallucinations, gastrointestinal disturbances. 2. Each drug deserves use up to tolerance before switching to another. 3. Combinations of drugs may be best—as for example, giving Artane for rigidity and central stimulation along with Hyoscine or Benadryl for tremor. 4. Atropine is a suitable choice for rigidity in the young, but is *never* to be used in the old because of the threat of glaucoma. 5. The most frequent side effects to be watched for in the use of many of these drugs—dryness of the mouth and blurring of vision. 6. In general, post-encephalitic types have tremendous tolerance for any drugs, arteriosclerotic types have least tolerance. 7. Artane or Pagitane are usually good drugs with which to start and, in general, are safe enough for any age group. 8. Spectacular initial response is not too unusual, but probably will "wear off" in time. This same response, though usually less spectacular, may be repeated on shifting to other drugs. 9. Hence, rotation of drugs is to be borne in mind in the care of these chronic patients. 10. Some of these drugs seem to have rather selective action—for example, for rigidity, Atropine, Artane, or Cogentin seem best; for tremor, Hyoscine, Benadryl, or Stramonium; for akinesia, Dexedrine or Artane; for oculogyria, Artane, Pagitane, or Atropine.

It is interesting to note that the *"old"* potato plant products and the *"new"* synthetics (both anti-spasmodics and anti-histaminics) bear some definite similarities in chemical structure (see structural formulas illustrated); hence their fairly similar effectiveness in Parkinsonism should come as no great surprise. Trasentine, developed during the 1930's in a search for a synthetic Atropine-like drug, was itself ineffectual in Parkinsonism but became the prototype of Artane and other effective synthetic anti-spasmodics. Interestingly, though, this same Trasentine which sparked the development of all the synthetic anti-spasmodics bears an even stronger chemical structural resemblance to Benadryl, the anti-histaminic (q.v.), than it does to Artane! This trend of chemical similarities in effective anti-Parkinson drugs is epitomized by Cogentin in that it combines the "virtues"—in this case, the active radicles—of Atropine (peer of the old potato plant products) and Benadryl (the anti-histaminic).

In connection with Cogentin, Himwich and Rinaldi[5], and other collaborators have done some interesting work lately in determining the site of action of this and related drugs. In studies on rabbits, they have found that Cogentin and other effective anti-Parkinson drugs seem to work at the level of the reticular system (a cholinergic system), by their anti-cholinergic action reducing or eliminating both the upstream as well as downstream effects of the activating system. Himwich points to this as a possible explanation for both the subjective and objective improvement in Parkinsonism patients on these drugs—in effect, a pharmacological lobotomy (diminishing the upstream arousal stimuli from the brain stem reticular formation) and a pharmacological tractotomy of the reticulo-spinal tracts (diminishing the downstream effect of theoretically 'released' extrapyramidal efferents). In this last, Himwich's theory clearly embraces the ideas of Jenkner and Ward and Falkerts and Spiegel described above. From this experience, Himwich has further suggested using the reticular activating system in this way for screening anti-Parkinson drugs developed in the future.

This has been a glimpse of Parkinsonism in 1958, one hundred and forty-one

years after James Parkinson wrote, with undaunted optimism and with words that still apply, "but, although, at present, uninformed as to the precise nature of the disease, still it ought not to be considered as one against which there exists no countervailing remedy" and then added, in saluting future investigators, "by their benevolent labours, its real nature may be ascertained and appropriate modes of relief, or even of cure, pointed out".

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RECTOSIGMOID ISCHEMIA IN SURGERY OF ABDOMINAL AORTIC ANEURYSMS

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The rectosigmoid area of the colon is singularily vulnerable to ischemia due to the anatomical characteristics of its arterial blood supply. The critical area of Sudeck[1] has been demonstrated both anatomically and clinically to be an important consideration when dealing with intrinsic lesions of this region. Another aspect of this problem has manifested itself with our increasing experience in the surgical management of abdominal aortic aneurysms. When resecting the abdominal aorta, it is usually necessary to sacrifice the inferior mesenteric artery and oftentimes one or both internal iliac arteries. The blood supply to the rectosigmoid colon may, under these circumstances, depending upon the adequacy of the collateral circulation, be so markedly diminished that the viability of this segment of colon is threatened. Major bowel complications have arisen from the ischemia produced in this manner. The advisability of maintaining the patency of at least one internal iliac artery following resection of an abdominal aortic aneurysm was pointed out by us previously.[2] A recent report by McKain and Shumacker[3] of two cases of severe ischemia of the left colon following resections of arteriosclerotic abdominal aneurysms serves to emphasize further the precarious nature of the arterial blood supply to the distal colon following aneurysmectomy. Moore[4] and Movius[5] have reported rectal strictures presumably related to ischemic changes produced by aortic bifurcation resection.

We have had experience in seventy-five resections for abdominal aortic aneurysm, with five patients who have clinically demonstrated varying degrees of ischemia of the rectosigmoid. These changes ranged from frank necrosis of the sigmoid and rectum to mucosal sloughing with transient bloody diarrhea. It is the purpose of this report to describe these cases and indicate the factors most likely responsible for their occurrence.

REPORT OF CASES

Case 1. W. M. was a 73 year old man in whom a large arteriosclerotic abdominal aneurysm was discovered during a cholecystectomy in 1949. The aneurysm became progressively larger and on 5-5-53 an aortogram was performed demonstrating it to be technically resectable. On 5-14-53 the patient underwent resection of his aneurysm which measured 22 x 22 cm. and extensively involved the left common iliac artery, including its bifurcation, and to a lesser degree the right common iliac artery. It was necessary to divide and ligate both the inferior mesenteric artery and the left internal iliac artery to accomplish satisfactory resection of the aneurysm. A homograft was used for replacement. The distal anastomosis on the left was made to the external iliac artery and on the right to the common iliac artery after first carrying out an intimectomy of its bifurcation. The graft was then wrapped in fascia lata and observed to function satisfactorily. Distal pulses were present postoperatively.

The immediate postoperative course was satisfactory. The patient regained consciousness and had a stable blood pressure of 120/70. Approximately twelve hours

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following operation a state of irreversible vascular collapse developed and the patient expired.

Postmortem examination revealed only extensive systemic arteriosclerosis. In addition, however, a 39 cm. segment of rectum and sigmoid colon was found to have undergone early necrosis with the significant changes starting 4 cm. from the anus. Undoubtedly this contributed to his death. The homograft was found to be intact and apparently functional except for the right internal iliac artery which had thrombosed.

Case 2. A. H. was a 62 year old man who was discovered to have a pulsating abdominal mass during a physical examination. An aortogram was carried out five weeks later on 11-11-54. This demonstrated a typical arteriosclerotic aneurysm. On 11-30-54 resection of the 10 x 20 cm. aneurysm with homograft replacement was satisfactorily accomplished. The aneurysm involved the right common iliac artery and was, therefore, included in the resection making it necessary to anastomose this limb of the graft to the right external iliac artery. The right internal iliac artery was tied. Due to the extensive arteriosclerotic changes in the left common iliac artery bifurcation it was necessary to intimectomize the distal stump into both the left internal iliac and external iliac arteries before an anastomosis could be accomplished. This was done in an attempt to preserve the function of the left internal iliac artery. The inferior mesenteric artery had, of course, been divided. Before circulation was re-established into the left iliac system, the rectum and lower sigmoid colon were observed to be cyanotic with the definite appearance of localized ischemia. After a 20 minute period following return of circulation into the left internal iliac artery, the condition of the rectosigmoid was considerably improved.

Postoperatively the patient's condition was atisfactory and he had good peripheral pulses. On the first postoperative day there was the onset of a bloody diarrhea. The first movements were tarry and later contained bright red blood. This was associated with fever to 103.4° F. but there was no evidence of peritonitis. With conservative management the diarrhea and blood disappeared by the fourth day. Unfortunately proctoscopic examination was not done. The patient's convalescence was otherwise uneventful and he was discharged following a postoperative aortogram which demonstrated a well functioning homograft on the nineteenth day after operation.

No further colon difficulty was experienced by the patient and a subsequent barium enema showed a good mucosal pattern of the left colon with no evidence of stricture in the rectosigmoid. He later died of a reticulum cell sarcoma of the stomach.

Case 3. C. K. is a 52 year old man who was referred for treatment of a known arteriosclerotic abdominal aneurysm. Operation was carried out on 10-5-57. The aneurysm was a large one with involvement of the right common iliac artery and to a lesser extent the left common iliac artery. Due to the marked adherence of the aneurysm to the vena cava and common iliac veins, the aneurysm wall was left intact at these locations. In spite of this precautionary measure of unroofing the aneurysm, the vena cava was entered with a resultant loss of blood and hypotension. Following resection, replacement was accomplished with a homograft; suturing the right limb of the graft to the external iliac artery and the left limb to the common iliac artery just proxi-

mal to its bifurcation. The right internal iliac artery and inferior mesenteric arteries were of necessity sacrificed.

The early postoperative course was complicated by sinus tachycardia, hypotension, and fever to 103° F. The blood pressure was supported by Levophed until the fourth day when it stabilized. Intravenous Achromycin was also given. On the ninth postoperative day he developed evidence of thrombophlebitis of the left leg and suffered a pulmonary infarct in the right lung with compatible x-ray changes. Heparin and Marcumar were administered and twenty-four hours later moderately severe bright red rectal bleeding occurred. The bleeding increased and the anticoagulants were stopped. Vitamin K therapy and transfusions were instituted. Because of the persistent severe rectal hemorrhage being possibly due to a perforation of the graft, the patient was operated upon. Vena caval ligation was done to protect against further pulmonary embolism. The homograft was found to be intact. No source of colon hemorrhage was discernable and the hemorrhage was felt to be due to an intrinsic colon lesion which had bled as a result of the anticoagulant therapy. Recovery from the procedure was gratifying and rectal bleeding subsided.

One week later the patient developed fever, severe rectal pain, and purulent diarrhea. Proctoscopic examination revealed an extensive purulent ulcerative proctitis. Stool cultures revealed only coliform and proteus organisms. Because of failure of the conservative management, a right transverse colostomy was done on 11-12-57. The colon appeared normal at this level. Rapid improvement followed the fecal stream diversion and the patient was discharged fifty-one days following his aneurysmectomy.

Since discharge his condition has continued to improve with weight gain and return of strength. The homograft continues to function satisfactorily with good peripheral pulses. There has been no marked leg swelling from the vena caval ligation. At present, proctoscopic and barium enema examinations reveal an almost complete obliteration, by structure and granulation, of the rectum starting 5 cm. from the anal verge and extending to the rectosigmoid. The future plan is to do a pull-through resection of his stricture followed by colostomy closure.

Case 4. B. D. is a 54 year old man who underwent a diagnostic laparotomy at another hospital in June 1957 at which time an arteriosclerotic abdominal aneurysm was discovered. No treatment was advised. The aneurysm ruptured while the patient was at work and he was immediately transported to our emergency room where the proper diagnosis was made and the patient taken to the operating room. Emergency laparotomy was carried out on 11-23-57 and a large ruptured aneurysm was found. There was a very extensive retroperitoneal and pelvic hematoma and free intraperitoneal blood. The aneurysm involved both common iliac arteries and was adherent to both iliac veins and the vena cava. After gaining control of the proximal aorta, the aneurysm was unroofed and because of the extensive involvement of the iliac arteries these were oversewn at the bifurcation level. It could not be determined if either the right or left internal iliac artery was functional. An elastic dacron prosthesis was used for replacement. Because of the amount of arteriosclerotic involvement of the iliac systems, making anastomoses at this level impossible, the limbs of the prosthesis were bypassed into the groin and end-to-side anastomosis made to each common femoral artery. Even the

common femoral arteries were found to be markedly arteriosclerotic. Fortunately the prosthesis functioned satisfactorily and the patient tolerated the operation surprisingly well.

The postoperative course was gratifying and essentially uncomplicated until the eleventh day when he developed evidence of thrombophlebitis in the left leg and also had the onset of diarrhea. Proctoscopic examination revealed a severe ulcerative proctitis. Because of the danger of rectal bleeding, a two week course of Heparin alone was given for the thrombophlebitis. The patient's diarrhea persisted and he ran a low-grade fever. At no time was there significant blood loss per rectum. Stool culture revealed coliform, proteus and streptococcus viridans organisms. Conservative management, which included sulfathaladine, was continued with gradual symptomatic improvement of the diarrhea and objective evidence of healing by proctoscopy. The peripheral pulses remained of good quality and the patient was discharged thirty-eight days following successful emergency aneurysmectomy.

The patient has been followed in the clinic with serial proctoscopic examinations which have shown complete healing of the rectal mucosa. There has been weight gain and complete return of normal bowel function. There remains, however, by barium enema, an area of narrowing 5 cm. in length at the junction of the rectum and sigmoid colon. Sigmoidoscopic examination reveals at 10 cm. a strictured area of rectosigmoid with satisfactory bowel lumen and intact mucosa. The patient has now returned to work and it is hoped that no further difficulty will arise from his colon deformity.

Case 5. H. C. is a 69 year old man who was well until one week before admission when he developed sudden severe back pain which radiated in a radicular manner to the lower abdomen and scrotum. This pain persisted, and in addition, he developed more abdominal discomfort with nausea and vomiting. He had also noted the passage of several bloody stools.

Physical examination at time of admission revealed a dehydrated, severely ill, elderly man with a blood pressure of 130/80. There was abdominal tenderness in both the RLQ and the LLQ but this seemed more acute on the left. Some widening of aortic pulsation was noted. Proctoscopic examination was carried out which showed an annular constriction at 15 cm. with an ulcerative, erythematous mucosal process extending distally into the rectum. The rectal mucosa was very friable and bled easily.

After hydration the hemoglobin was 15.8 cm., WBC 15,350 and his urine showed 1+ albumin with an occasional hyalin cast. Intravenous pyelograms demonstrated only a double collecting system on the left and no other abnormalities. Emergency barium enema revealed no colon obstruction or other specific lesions but did strongly suggest the presence of an arteriosclerotic aneurysm. Because of the appearance of the sigmoid colon, which showed a lack of normal mucosal pattern, arterial insufficiency to this area was suggested.

Because of the lack of clinical improvement, and the likelihood of a leaking aneurysm being present, the patient was operated upon 3-11-58. A moderate sized arteriosclerotic aortic aneurysm was found with evidence of rupture into the left retroperitoneal tissues. There was an extensive inflammatory change associated with the extravasated blood. As was later demonstrated during dissection and ligation of

the inferior mesenteric artery, it had been occluded by this process. The sigmoid colon and upper rectum were somewhat cyanotic, contracted, and had the appearance of being viable but definitely ischemic. Resection of the aneurysm was carried out utilizing an elastic dacron prosthesis for replacement. The distal limbs were sutured in an end-to-side manner into the common iliac arteries at the bifurcation level. There was considerable arteriosclerotic involvement of the internal iliac arteries and their functional status was not known. The prosthesis worked well with satisfactory peripheral pulses present at the termination of the operation.

Postoperatively it was necessary to sustain the blood pressure with vasopressors for twenty-four hours. Aside from some difficulty with chest secretions, patient's convalescense was completely uncomplicated except for a superficial wound infection. Two proctoscopic examinations failed to show any residual rectal ulcerations. The patient has had no diarrhea or bowel disfunction. He was discharged thirty-one days following his aneurysmectomy.

COMMENT

It seems evident that the cases described clearly demonstrate that significant ischemia of the rectosigmoid colon may be produced when interruption of the inferior mesenteric artery, and one or both internal iliac arteries, occurs during abdominal aneurysmectomy. The collateral circulation that is available, and its efficiency in preventing serious colon complications under these circumstances, is of special interest.

It has been well established that in most instances a functioning inferior mesenteric artery may be ligated at or near its orgin with relative impunity. Collateral circulation is readily established to the sigmoid and rectum by way of the marginal artery of Drummond, an extension of the superior mesenteric system through middle colic branches, and the middle and inferior hemorrhoidal branches of the internal iliac arteries. When in addition, one of the internal iliac arteries is also ligated, the collateral circulation becomes more dependent upon the cross connections between the two internal iliac systems and also upon peripheral connections in the ligated internal iliac system such as the superior and inferior guteal, obturator, and iliolumbar arteries. If both internal iliac arteries are ligated along with the inferior mesenteric artery even greater reliance is placed upon the marginal artery and the above described collateral connections of the internal iliac system by way of the lumbar, circumflex iliac, and circumflex branches of the deep femoral artery. The collateral system of the inferior hemorrhoidal arteries, through their pudental connections, is apparently adequate for the limited anal segment but can not be expected to contribute significantly to the blood supply of the rectosigmoid colon.

It is worthy of comment, that when dealing with aneurysmal disease of the abdominal aorta one is more often faced with the necessity of interrupting functional arteries than when performing resections for occlusive disease. Certainly, if the inferior mesenteric artery is occluded by an atheromatous process prior to aortic bifurcation resection, there will have been an opportunity for the natural collateral blood supply to develop which will undoubtedly make its sacrifice less apt to produce any significant degree of ischemia. It is of interest that we have not observed one instance of bowel ischemia in aortic resections done for occlusive disease alone, while all of the cases

cited in this report had patent aneurysmal aortas and, therefore, lacked the physiological stimulus to develop a substantial collateral network prior to aneurysmectomy.

This same principal also applies to the internal iliac vessels. As illustrated by our cases, one may often be obligated to ligate a diseased but functioning internal iliac artery because of its involvement in the aneurysmal process. In fact, as shown in our fourth case, the aneurysm was so extensive that doing a long bilateral bypass to the common femoral arteries was the only possible choice. In this situation, retograde filling of the diseased iliac arteries was apparently not favorable enough for the establishment of an adequate collateral circulation.

Other factors also may function impair circulation to the sigmoid and rectum. A diffusely diseased internal iliac system will markedly reduce its efficiency and certainly make it more vulnerable to thrombosis, especially when the aorta is clamped, or during a hypotensive episode. Also, if an anastomosis is made to a diseased internal iliac artery, there is always risk of thrombosis. This is more apt to occur in our experience if intimectomy has been done, as in our first case.

There are certain precautions that should be observed in an attempt to prevent these distressing complications. It would seem axiomatic that at least the function of one internal iliac artery must be preserved if at all possible, preferably the left one. Care must be taken to avoid prolonged clamping of the aorta and periods of hypotension that may promote thrombosis in a part of the collateral system. Sufficient distal heparinzation is, of course, essential. Also, as the surgeon is readily able to observe the state of the circulation in the rectosigmoid, he should carefully evaluate this segment of colon during aortic occlusion and after re-establishment of the blood flow. The improvement in the appearance of the bowel in our second case following insertion of the graft was very striking. If this should not occur, prophylactic resection of the impaired colon or colostomy may be mandatory.

Rectosigmoid ischemia, produced by an arteriosclerotic abdominal aneurysm, may present itself as a diagnostic problem as illustrated by our fifth case. Abdominal symptoms associated with a bloody diarrhea for one week strongly suggested the presence of a primary colon lesion. As was observed at laparotomy, rupture of the aneurysm had produced an occlusion of the inferior mesenteric artery with the extravasated blood in the mesosigmoid further impairing the circulation of the rectosigmoid. Fortunately aneurysmectomy allowed return of an adequate circulation and uncomplicated recovery ensued.

SUMMARY AND CONCLUSIONS

Five cases are presented illustrating various degrees of rectosigmoid ischemia associated with surgery for arteriosclerotic abdominal aneurysms.

When the inferior mesenteric artery is interrupted, the collateral circulation from the marginal artery of the colon and the hemorrhoidal branches of the internal iliac arteries may be adequate but at times it is not. Sacrifice of one or both internal iliac arteries increases the risk of ischemia and, therefore, care should be taken to preserve at least one, and if possible, both of these arteries during aneurysmectomy.

Surgeons confronted with these cases should be aware of this possible complication and be prepared to take whatever steps are necessary, which may include bowel resection, to protect properly the patient so afflicted.

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